



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : <b>C07H 19/167, A61K 31/70</b>		<b>A1</b>	(11) International Publication Number: <b>WO 00/23457</b>
			(43) International Publication Date: 27 April 2000 (27.04.00)
(21) International Application Number: <b>PCT/IB99/01629</b>		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 5 October 1999 (05.10.99)		<b>Published</b> <i>With international search report.</i>	
(30) Priority Data: 9822702.8                      16 October 1998 (16.10.98)      GB 9825383.4                      19 November 1998 (19.11.98)      GB 9908931.0                      19 April 1999 (19.04.99)          GB			
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(54) Title: ADENINE DERIVATIVES			
<div style="text-align: right;">(I)</div>			
(57) Abstract			
<p>The present invention provides compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof, together with processes for the preparation of, compositions containing, uses of and intermediates used in the preparation of, such compounds that have adenosine A2 a receptor agonist activity.</p>			

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### ADENINE DERIVATIVES

The present invention relates to certain adenine derivatives that are selective, functional agonists of the human adenosine A2a receptor, to their preparation, and to compositions and uses thereof. The compounds and compositions may be used as anti-inflammatory agents in the treatment of, *inter alia*, diseases of the respiratory tract.

Adenosine is a ubiquitous molecule having a central role in mammalian intermediary metabolism. Independently, adenosine acts on multiple surface receptors to produce a variety of responses. Receptor classification has revealed the presence of at least four subtypes: A1, A2a, A2b and A3. Stimulation of adenosine A2 receptors on the surface of human neutrophils has been reported to potently inhibit a range of neutrophil functions. Activated neutrophils can damage lung tissue by release of reactive oxygen species, such as superoxide anion radicals ( $O_2^{\cdot-}$ ), and granule products, such as human neutrophil elastase (HNE), amongst other inflammatory mediators. In addition, activated neutrophils perform both *de novo* synthesis and release of arachidonate products such as leukotriene  $B_4$  ( $LTB_4$ ).  $LTB_4$  is a potent chemo-attractant that recruits additional neutrophils to the inflammatory focus, whereas released  $O_2^{\cdot-}$  and HNE adversely affect pulmonary extracellular matrix. The A2 receptor subtype mediating many of these responses ( $O_2^{\cdot-}$  and  $LTB_4$ /HNE release and cell adhesion) is established as A2a. The A2 subtype (A2a or A2b) mediating the other effects remains to be established.

Selective agonist activity at the A2a receptor is considered to offer greater therapeutic benefit than non-selective adenosine receptor agonists because interaction with other receptor subtypes is associated with detrimental effects in the lung in animal models and human tissue studies. For example, asthmatics, but not non-asthmatics, bronchoconstrict when challenged with inhaled adenosine. This response is at least in part due to the activation of the A1 receptor subtype. Activation of A1 receptors also promotes neutrophil

chemotaxis and adherence to endothelial cells, thus promoting lung injury. Furthermore, many patients with respiratory disease will be co-prescribed  $\beta_2$ -agonists, and negative interaction has been shown in animal studies between isoprenaline and adenosine receptors negatively coupled to adenylate cyclase.

5 Degranulation of human mast cells is promoted by activation of adenosine A2b receptors, thus selectivity over this receptor is also advantageous.

We have now surprisingly found the present adenine derivatives inhibit neutrophil function and are selective agonists of the adenosine A2a receptor.

10

The present compounds may be used to treat any disease for which an adenosine A2a receptor agonist is indicated. They can be used to treat a disease where leukocyte (e.g. neutrophil, eosinophil, basophil, lymphocyte, macrophage) -induced tissue damage is implicated. They are useful as anti-

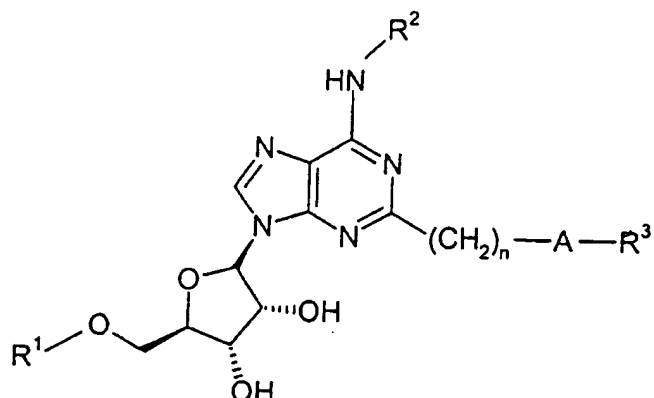
15 inflammatory agents in the treatment of diseases of the respiratory tract such as adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis. The present compounds may also be used in the treatment of septic shock, male erectile dysfunction,

20 hypertension, stroke, epilepsy, cerebral ischemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Helicobacter pylori*-gastritis, non-*Helicobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced

25 damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing.

Accordingly, in one aspect the present invention provides a compound of formula (I):

30



10 wherein

R¹ is alkyl or cyclopropylmethyl;

R² is phenyl-alkylene or naphthyl-alkylene, said alkylene chain being optionally further substituted by phenyl or naphthyl, each phenyl or naphthyl being

15 optionally substituted by one or more substituents each independently selected from alkyl, alkoxy, halo and cyano;

n is 1 or 2;

20 A is NR<sup>a</sup>, NR<sup>a</sup>C(O), NR<sup>a</sup>C(O)NR<sup>a</sup>, NR<sup>a</sup>C(O)O, OC(O)NR<sup>a</sup>, C(O)NR<sup>a</sup>, NR<sup>a</sup>SO<sub>2</sub>, SO<sub>2</sub>NR<sup>a</sup>, O, S or SO<sub>2</sub>;

R<sup>a</sup> is H, alkyl or benzyl optionally ring-substituted by one or more substituents each independently selected from alkyl, alkoxy, halo and cyano;

25

R³ is a group of the formula -(CH<sub>2</sub>)<sub>p</sub>-R<sup>p</sup>-B;

p is 0, 1 or 2;

30 R<sup>p</sup> is a bond, alkylene, cycloalkylene, phenylene or naphthylene, said cycloalkylene, phenylene and naphthylene each being optionally substituted by one or more substituents each independently selected from alkyl, alkoxy, halo

and alkoxyalkylene;

B is

- (i) H,  $-NR^bR^b$ ,  $R^bR^bN$ -alkylene,  $-OR^b$ ,  $-COOR^b$ ,  $-OCOR^b$ ,  $-SO_2R^b$ ,  $-CN$ ,  $-SO_2NR^bR^b$ ,  $-NR^bCOR^b$ ,  $-NR^bSO_2R^b$  or  $-CONR^bR^b$ , in which each  $R^b$  is the same or different and is selected from H, alkyl, phenyl and benzyl, provided that,
- (a) when B is  $-OCOR^b$ ,  $-SO_2R^b$ ,  $-NR^bCOR^b$  or  $-NR^bSO_2R^b$ , then the terminal  $R^b$  is not H, and,
- (b)  $R^p$  is a bond, p is 0 and B is H only when A is  $NR^a$ ,  $NR^aC(O)NR^a$ ,  $OC(O)NR^a$ ,  $C(O)NR^a$ ,  $SO_2NR^a$ , O or S,
- (ii) an optionally-substituted, fully- or partially-saturated or -unsaturated, mono- or bicyclic, heterocyclic group, which is linked to  $R^p$  by a ring carbon atom, or
- (iii) N-linked azetidiny, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl, each optionally substituted by one or more alkyl substituents, with the proviso that  $-(CH_2)_p-R^p$  is not  $-CH_2-$ ; and

where A is  $NR^a$ ,  $C(O)NR^a$ ,  $OC(O)NR^a$  or  $SO_2NR^a$ ,  $R^a$  and  $R^3$  taken together with the nitrogen atom to which they are attached can form an azetidine, pyrrolidine, piperidine or piperazine ring, optionally substituted by one or more alkyl substituents:

and pharmaceutically acceptable salts and solvates thereof.

In a second aspect the present invention provides a compound of the formula (I) wherein

$R^1$  is  $C_1$ - $C_6$  alkyl or cyclopropylmethyl;

$R^2$  is phenyl- $(C_1$ - $C_6)$ -alkylene or naphthyl- $(C_1$ - $C_6)$ -alkylene, said  $C_1$ - $C_6$  alkylene chain being optionally further substituted by phenyl or naphthyl, each phenyl or

naphthyl being optionally substituted by one or more substituents each independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo and cyano;

n is 1 or 2;

5

A is NR<sup>a</sup>, NR<sup>a</sup>C(O), NR<sup>a</sup>C(O)NR<sup>a</sup>, NR<sup>a</sup>C(O)O, OC(O)NR<sup>a</sup>, C(O)NR<sup>a</sup>, NR<sup>a</sup>SO<sub>2</sub>, SO<sub>2</sub>NR<sup>a</sup>, O, S or SO<sub>2</sub>;

10 R<sup>a</sup> is H, C<sub>1</sub>-C<sub>6</sub> alkyl or benzyl optionally ring-substituted by one or more substituents each independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo and cyano;

R<sup>3</sup> is a group of the formula -(CH<sub>2</sub>)<sub>p</sub>-R<sup>p</sup>-B;

15 p is 0, 1 or 2;

R<sup>p</sup> is a bond, C<sub>1</sub>-C<sub>6</sub> alkylene, C<sub>3</sub>-C<sub>7</sub> cycloalkylene, phenylene or naphthylene, said C<sub>3</sub>-C<sub>7</sub> cycloalkylene, phenylene and naphthylene each being optionally substituted by one or more substituents each independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo and C<sub>1</sub>-C<sub>6</sub> alkoxy-C<sub>1</sub>-C<sub>6</sub>-alkylene;

20

B is

- (i) H, -NR<sup>b</sup>R<sup>b</sup>, R<sup>b</sup>R<sup>b</sup>N-(C<sub>1</sub>-C<sub>6</sub>)-alkylene, -OR<sup>b</sup>, -COOR<sup>b</sup>, -OCOR<sup>b</sup>, -SO<sub>2</sub>R<sup>b</sup>, -CN, -SO<sub>2</sub>NR<sup>b</sup>R<sup>b</sup>, -NR<sup>b</sup>COR<sup>b</sup>, -NR<sup>b</sup>SO<sub>2</sub>R<sup>b</sup> or -CONR<sup>b</sup>R<sup>b</sup>, in which each R<sup>b</sup> is the same or different and is selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl and benzyl, provided that,
- 25 (a) when B is -OCOR<sup>b</sup>, -SO<sub>2</sub>R<sup>b</sup>, -NR<sup>b</sup>COR<sup>b</sup> or -NR<sup>b</sup>SO<sub>2</sub>R<sup>b</sup>, then the terminal R<sup>b</sup> is not H, and,
- (b) R<sup>p</sup> is a bond, p is 0 and B is H only when A is NR<sup>a</sup>, NR<sup>a</sup>C(O)NR<sup>a</sup>, OC(O)NR<sup>a</sup>, C(O)NR<sup>a</sup>, SO<sub>2</sub>NR<sup>a</sup>, O or S,
- 30 (ii) an optionally-substituted, fully- or partially-saturated or -unsaturated, mono- or bicyclic, heterocyclic group, which is linked to R<sup>p</sup> by a ring

carbon atom, or

- (iii) N-linked azetidiny, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl, each optionally substituted by one or more C<sub>1</sub>-C<sub>6</sub> alkyl substituents, with the proviso that  $-(CH_2)_p-R^p$  is not  $-CH_2-$ ; and

5

where A is NR<sup>a</sup>, C(O)NR<sup>a</sup>, OC(O)NR<sup>a</sup> or SO<sub>2</sub>NR<sup>a</sup>, R<sup>a</sup> and R<sup>3</sup> taken together with the nitrogen atom to which they are attached can form an azetidine, pyrrolidine, piperidine or piperazine ring, each optionally substituted by one or more C<sub>1</sub>-C<sub>6</sub> alkyl substituents:

10

and pharmaceutically acceptable salts and solvates thereof.

In a third aspect the present invention provides a compound of the formula (I) wherein

15

R<sup>1</sup> is alkyl or cyclopropylmethyl;

R<sup>2</sup> is phenyl-alkylene or naphthyl-alkylene where the alkylene chain may be substituted with methyl, ethyl, phenyl or naphthyl;

20

n is 1 or 2; and

A is NR<sup>a</sup>, NR<sup>a</sup>C(O), NR<sup>a</sup>C(O)NR<sup>a</sup>, NR<sup>a</sup>C(O)O, OC(O)NR<sup>a</sup>, C(O)NR<sup>a</sup>, NR<sup>a</sup>SO<sub>2</sub>, SO<sub>2</sub>NR<sup>a</sup>, O, S or SO<sub>2</sub>, in which R<sup>a</sup> is H or alkyl;

25

R<sup>3</sup> is a group of the formula  $-(CH_2)_p-R^p-B$ , wherein p is 0, 1 or 2;

R<sup>p</sup> is a bond, or is alkylene, optionally alkyl-substituted cycloalkylene, phenylene or naphthylene; and

30

B is (i) H, -NR<sup>b</sup>R<sup>b</sup>, -OR<sup>b</sup>, -COOR<sup>b</sup>, -OCOR<sup>b</sup>, -SO<sub>2</sub>R<sup>b</sup>, -CN, -SO<sub>2</sub>NR<sup>b</sup>R<sup>b</sup>, -NR<sup>b</sup>COR<sup>b</sup>



or  $-\text{CONR}^b\text{R}^b$ , in which each  $\text{R}^b$  is the same or different and is selected from H and alkyl, provided that, (a) when B is  $-\text{SO}_2\text{R}^b$  or  $-\text{NR}^b\text{COR}^b$ , then the terminal  $\text{R}^b$  is other than H, and, (b)  $\text{R}^p$  is a bond, p is 0 and B is H only when A is  $\text{NR}^a$ ,  $\text{NR}^a\text{C}(\text{O})\text{NR}^a$ ,  $\text{C}(\text{O})\text{NR}^a$ ,  $\text{SO}_2\text{NR}^a$ , O or S, or (ii) B is an optionally-substituted,  
5 fully or partially saturated or unsaturated mono- or bicyclic heterocyclic group, each of which is linked through a ring carbon atom;

and pharmaceutically acceptable salts and solvates thereof.

10 In the above definitions, halo means fluoro, chloro, bromo or iodo. Alkyl, alkoxy and alkylene groups containing the requisite number of carbon atoms can be unbranched- or branched-chain. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy  
15 and t-butoxy. Examples of alkylene include methylene, 1,1-ethylene, 1,2-ethylene, 1,3-propylene and 1,2-propylene. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Examples of cycloalkylene include cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene and cycloheptylene.

20

The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts  
25 and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate and pamoate salts.

30

Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

- 5 For a review on suitable salts see Berge et al., J. Pharm. Sci., 66, 1-19, 1977.

The pharmaceutically acceptable solvates of the compounds of the formula (I) include the hydrates thereof.

- 10 Also included within the present scope of the compounds of the formula (I) are polymorphs thereof.

- A compound of the formula (I) may contain one or more additional asymmetric carbon atoms and therefore exist in two or more stereoisomeric forms. The  
15 present invention includes the individual stereoisomers of the compounds of the formula (I) together with mixtures thereof.

- Separation of diastereoisomers and cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or  
20 H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding  
25 diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

- In the definition of B, said optionally-substituted, fully- or partially-saturated or -unsaturated, mono- or bicyclic, heterocyclic group, which is linked to R<sup>p</sup> by a  
30 ring carbon atom, preferably has from 4 to 12 ring atoms, preferably from 4 or 5 to 10 ring atoms, each independently selected from C, N, O and S. More preferably, said group has ring atoms selected from 1 to 4 N atoms, 1 or 2 O

and 1 or 2 S atoms, with the remaining ring atoms being C atoms. Most preferably, said group has from 1 to 4 ring N atoms, or 1 or 2 ring N atoms and 1 O or 1 S ring atom, or 1 O or 1 S ring atom, with the remaining ring atoms being C atoms.

5

Examples of fully-unsaturated, that is heteroaryl, groups include imidazolyl, triazolyl, thienyl, furyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl and quinoxalinyl.

10

Examples of partially-saturated or -unsaturated heterocyclic groups include 1,2-dihydroisoquinolinyl, 3,4-dihydroisoquinolinyl and 1,2,3,4-tetrahydroisoquinolinyl.

15 Examples of fully-saturated heterocyclic groups include azetidiny, pyrrolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, morpholinyl and piperazinyl.

Said heterocyclic groups can be optionally substituted by one or more  
20 substituents each independently selected from  $R^5$ ,  $-OR^5$ , halo, oxo, hydroxy, cyano,  $-COR^5$ ,  $-COOH$ ,  $-COOR^5$ ,  $-CONH_2$ ,  $-CONHR^5$ ,  $-CONR^5R^5$ , amino,  $-NHR^5$ ,  $-NR^5R^5$ ,  $-SO_2R^5$ ,  $-SO_2NH_2$ ,  $-SO_2NHR^5$ ,  $-SO_2NR^5R^5$ ,  $-NHCOR^5$ ,  $-NR^5COR^5$ ,  $-NHSO_2R^5$ ,  $-NR^5SO_2R^5$  and pyridinyl,

25 wherein  $R^5$  is  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_7$  cycloalkyl, phenyl or naphthyl, each optionally substituted by  $C_3$ - $C_7$  cycloalkyl,  $C_1$ - $C_6$  alkoxy, halo, phenyl, naphthyl or benzylamino.

Preferably,  $R^1$  is  $C_1$ - $C_6$  alkyl.

30 Preferably,  $R^1$  is methyl.

Preferably,  $R^2$  is phenyl- $(C_1$ - $C_6)$ -alkylene, said  $C_1$ - $C_6$  alkylene chain being

optionally further substituted by phenyl.

Preferably, R<sup>2</sup> is 2-phenylethyl, said ethyl chain being optionally further substituted by phenyl.

Preferably, R<sup>2</sup> is 2-phenylethyl or 2,2-diphenylethyl.

5 Preferably, R<sup>2</sup> is 2,2-diphenylethyl.

Preferably, A is NR<sup>a</sup>, NR<sup>a</sup>C(O), NR<sup>a</sup>C(O)O, C(O)NR<sup>a</sup>, NR<sup>a</sup>SO<sub>2</sub>, SO<sub>2</sub>NR<sup>a</sup>, O, S or SO<sub>2</sub>.

Preferably, A is NR<sup>a</sup> or NR<sup>a</sup>SO<sub>2</sub>.

10

Preferably, R<sup>a</sup> is H, C<sub>1</sub>-C<sub>6</sub> alkyl or benzyl optionally ring-substituted by one or more C<sub>1</sub>-C<sub>6</sub> alkoxy substituents.

Preferably, R<sup>a</sup> is H, methyl, 2-methylprop-1-yl or methoxybenzyl.

Preferably, R<sup>a</sup> is H, methyl, 2-methylprop-1-yl or 2-methoxybenzyl.

15

Preferably, R<sup>3</sup> is

H,

C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted by C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, amino, -NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -CONH<sub>2</sub>, -CONH(C<sub>1</sub>-C<sub>6</sub> alkyl), -CON(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, phenyl (optionally substituted by halo, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy-(C<sub>1</sub>-C<sub>6</sub>)-alkylene, amino-(C<sub>1</sub>-C<sub>6</sub>)-alkylene, cyano or piperidinyl (optionally substituted by C<sub>1</sub>-C<sub>6</sub> alkyl, halo-(C<sub>1</sub>-C<sub>6</sub>)-alkyl or halo-(C<sub>1</sub>-C<sub>6</sub>)-alkanoyl)), piperidinyl or tetrahydropyranyl,

20 C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted by C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, benzylamino or C<sub>1</sub>-C<sub>6</sub> alkanesulphonamido,

phenyl optionally substituted by halo, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy-(C<sub>1</sub>-C<sub>6</sub>)-alkylene, amino-(C<sub>1</sub>-C<sub>6</sub>)-alkylene or piperidinyl (optionally substituted by C<sub>1</sub>-C<sub>6</sub> alkyl, halo-(C<sub>1</sub>-C<sub>6</sub>)-alkyl or halo-(C<sub>1</sub>-C<sub>6</sub>)-alkanoyl), or

azetidiny, pyridiny, piperidiny, tetrahydrothiopyranyl or 1,2,3,4-

30 tetrahydroisoquinolinyl, each optionally substituted by C<sub>1</sub>-C<sub>6</sub> alkyl, benzhydryl, halo-(C<sub>1</sub>-C<sub>6</sub>)-alkanoyl, oxo, hydroxy, cyano, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, benzoyl or pyridiny.

Preferably, R<sup>3</sup> is H, methyl, n-propyl, i-propyl, 2-methylprop-1-yl, 2,2-dimethylprop-1-yl, n-butyl, t-butyl, pentan-3-yl, cyclopentyl, cyclohexyl, 4-(isopropyl)cyclohexyl, cyclopropylmethyl, cyclohexylmethyl, 2-methoxyethyl, 2-dimethylaminoethyl, 2-(N,N-dimethylcarbamoyl)ethyl, N,N-(diisopropyl)carbamoylmethyl, 2-(N-t-butylcarbamoyl)ethyl, phenyl, benzyl, 4-chlorobenzyl, 2-methoxybenzyl, 3,4-dimethoxybenzyl, 4-(isopropoxy)benzyl, 2-methoxymethylbenzyl, 4-aminomethylbenzyl, 4-cyanobenzyl, 4,4-dimethylcyclohexyl, 4-methoxycyclohexyl, 4-benzylaminocyclohexyl, 4-methanesulphonamidocyclohexyl, 2-piperidinoethyl, 4-(piperidin-4-yl)phenyl, 4-(1-trifluoroacetyl)piperidin-4-yl)phenyl, 1-benzhydrylazetid-3-yl, 2,6-dimethylpyridin-3-yl, 5-cyanopyridin-2-yl, 1-methylpiperidin-4-yl, 1-(isopropyl)piperidin-4-yl, 1-t-butoxycarbonylpiperidin-4-yl, 1-benzoylpiperidin-4-yl, 1-(2-pyridinyl)piperidin-4-yl, 1,1-dioxotetrahydrothiopyran-4-yl, tetrahydropyran-4-ylmethyl, 5-methyl-1,2,3,4-tetrahydroisoquinolin-8-yl or 5-methyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-8-yl.

Preferably, R<sup>3</sup> is phenyl, cyclohexyl, 5-methyl-1,2,3,4-tetrahydroisoquinolin-8-yl, 2-methylprop-1-yl, i-propyl, 2-methoxybenzyl or N,N-(diisopropyl)carbamoylmethyl.

20

Preferably, -A-R<sup>3</sup> is amino, isopropylamino, pentan-3-ylamino, 2-methylprop-1-ylamino, di(2-methylprop-1-yl)amino, N-cyclohexyl-N-methylamino, 2-methoxyethylamino, 2-(N,N-dimethylcarbamoyl)ethylamino, N,N-(diisopropyl)carbamoylmethylamino, 2-(N-t-butylcarbamoyl)ethylamino, cyclopentylamino, cyclohexylamino, 4,4-dimethylcyclohexylamino, 4-(isopropyl)cyclohexylamino, 4-methoxycyclohexylamino, cis-4-methoxycyclohexylamino, trans-4-methoxycyclohexylamino, 4-benzylaminocyclohexylamino, trans-4-benzylaminocyclohexylamino, 4-methanesulphonamidocyclohexylamino, trans-4-methanesulphonamidocyclohexylamino, cyclopropylmethylamino, cyclohexylmethylamino, benzylamino, 4-chlorobenzylamino, 2-methoxybenzylamino, di(2-methoxybenzyl)amino, 4-(isopropoxy)benzylamino,

30

3,4-dimethoxybenzylamino, 2-methoxymethylbenzylamino, 4-aminomethylbenzylamino, 4-cyanobenzylamino, 1-benzhydrylazetid-3-ylamino, 2,6-dimethylpyridin-3-ylamino, 5-cyanopyridin-2-ylamino, 1-methylpiperidin-4-ylamino, 1-(isopropyl)piperidin-4-ylamino, 1-(t-butoxycarbonyl)piperidin-4-ylamino, 1-benzoylpiperidin-4-ylamino, 1-(pyridin-2-yl)piperidin-4-ylamino, 2-piperidinoethylamino, 1,1-dioxotetrahydrothiopyran-4-ylamino, benzamido, phenylacetamido, t-butoxycarbonylamino, methanesulphonamido, n-propylsulphonylamido, i-propylsulphonylamido, n-butylsulphonamido, 2-methylprop-1-ylsulphonamido, 2,2-dimethylprop-1-ylsulphonamido, 2-methoxyethylsulphonamido, phenylsulphonylamido, benzylsulphonamido, 4-(piperidin-4-yl)phenylsulphonylamido, 4-(1-trifluoroacetyl)piperidin-4-yl)phenylsulphonylamido, tetrahydropyran-4-ylmethylsulphonamido, 5-methyl-1,2,3,4-tetrahydroisoquinolin-8-ylsulphonylamido, 5-methyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-8-ylsulphonylamido, benzylaminosulphonyl, 2-(N,N-dimethylamino)ethoxy, benzyloxy, 2-piperidinoethoxy, 1-methylpiperidin-4-yloxy, phenylthio, benzylthio or benzylsulphonyl, or is 4-isopropylpiperidinocarbonyl.

Preferably, -A-R<sup>3</sup> is phenylsulphonamido, cyclohexylamino, 5-methyl-1,2,3,4-tetrahydroisoquinolin-8-ylsulphonylamido, 2-methylprop-1-ylamino, i-propylamino, 2-methoxybenzylamino, N,N-(diisopropyl)carbamoylmethylamino or 2-methylprop-1-ylsulphonamido.

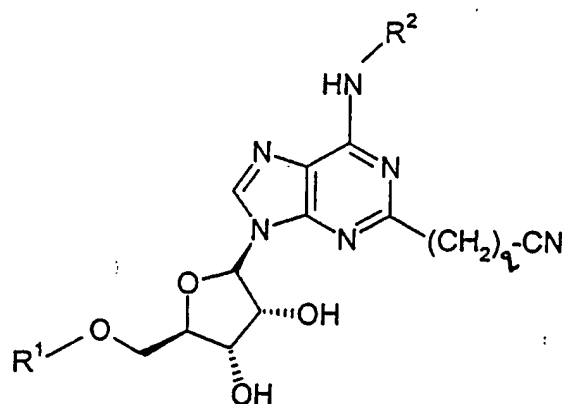
Preferred examples of compounds of the formula (I) include those of the Examples section hereafter, including any pharmaceutically acceptable salts thereof.

The compounds of the formula (I) can be prepared by conventional routes such as by the procedures described in the general methods presented below or by the specific methods described in the Examples section, or by similar methods thereto. The present invention also encompasses any one or more of these processes for preparing the compounds of formula (I), in addition to any novel intermediates used therein. In the general methods described, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, A and

n are as previously described for a compound of the formula (I) unless otherwise stated.

Compounds of formula (I) may be prepared by reduction of the corresponding  
5 compound of formula (IIA):

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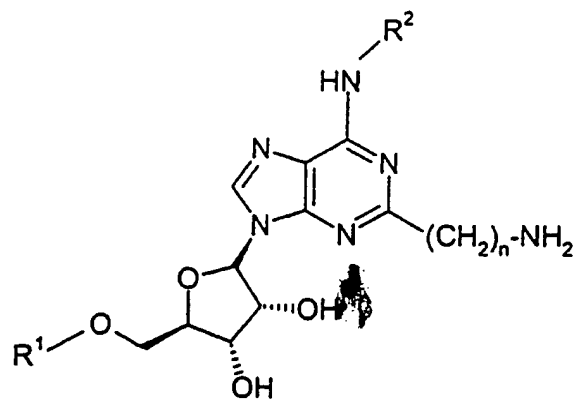


15

(IIA)

wherein q is n-1, using a reducing agent, such as by catalytic hydrogenation  
(e.g. with palladium-on-carbon), in a suitable solvent such as an alcohol (e.g.  
20 ethanol), optionally in the presence of ammonia, to form the corresponding  
compound of formula (IA), which is a compound of formula (I) wherein A is -NH  
and R³ is -H:

25



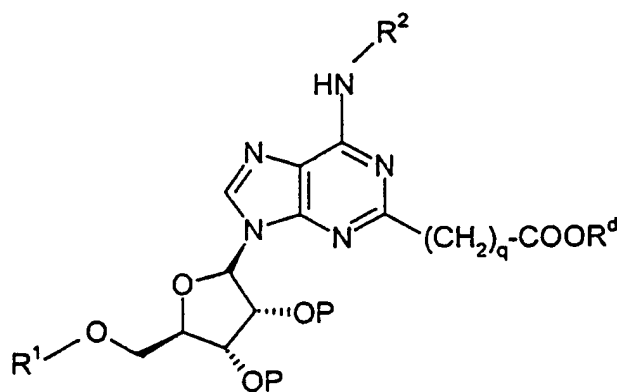
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(IA)

and thereafter optionally converting the compound of formula (IA) so prepared to another compound of formula (I) or salt thereof.

Conversion of the  $-(CH_2)_nNH_2$  group of formula (IA) may take place by methods known to those skilled in the art. A suitable method to prepare compounds of formula (I) wherein A is  $-NHCO-$  or  $-NHSO_2$  comprises reaction of the corresponding compound of formula (IA) with a compound of formula  $X-(CO$  or  $SO_2)-R^3$  wherein X is a leaving group, such as halo (especially chloro), in the presence of an acid acceptor, such as triethylamine, and in a suitable inert solvent, such as tetrahydrofuran (THF) or dichloromethane. Alternatively, where a compound of the formula (I) wherein A is  $NHSO_2$  is required, 2,6-lutidine may be utilised as both the acid acceptor and the solvent. Other standard methods may be used to convert the  $(CH_2)_nNH_2$  group to those wherein A is  $-NR^a$  (e.g., using a compound of the formula halo- $R^3$ , where halo is preferably chloro, or where p is 2,  $R^p$  is a bond and B is  $-CONR^bR^b$ , a suitable acrylamide derivative),  $-NR^aCO$ ,  $-NR^aCONR^a$ ,  $-NR^aCOO$  (e.g., by reaction with a suitable dicarbonate derivative) and  $-NR^aSO_2$ .

Alternatively, the corresponding compound of formula (IIA) may be subjected to nitrile hydrolysis, using standard methods, followed by protection of the reactive hydroxy/carboxyl groups to form the corresponding protected ester of formula (IIB):



(IIB)



wherein P is a protecting group, preferably *tert*-butyldimethylsilyl chloride (TBDMS);

R<sup>d</sup> is H or alkyl; and

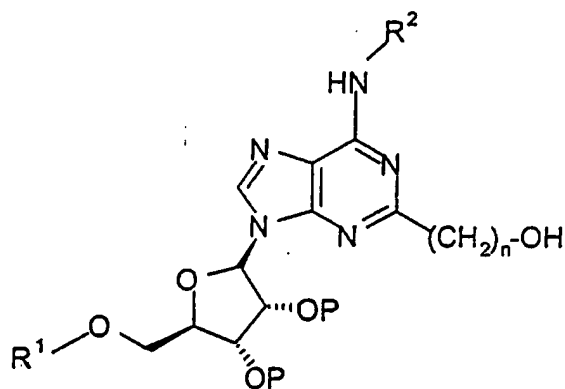
q is as defined for formula (IIA).

5

Thereafter, the compound of formula (IIB) may be reduced using a reducing agent, such as a metal hydride (e.g. lithium borohydride), to form the corresponding compound of formula (IB), which is a protected compound of formula (I) wherein A is -O- and R<sup>3</sup> is H:

10

15



(IB)

20

wherein P is as hereinbefore defined;

and thereafter, either prior to or after deprotection, optionally converting the compound of formula (IB) so prepared to another compound of formula (I) or salt thereof.

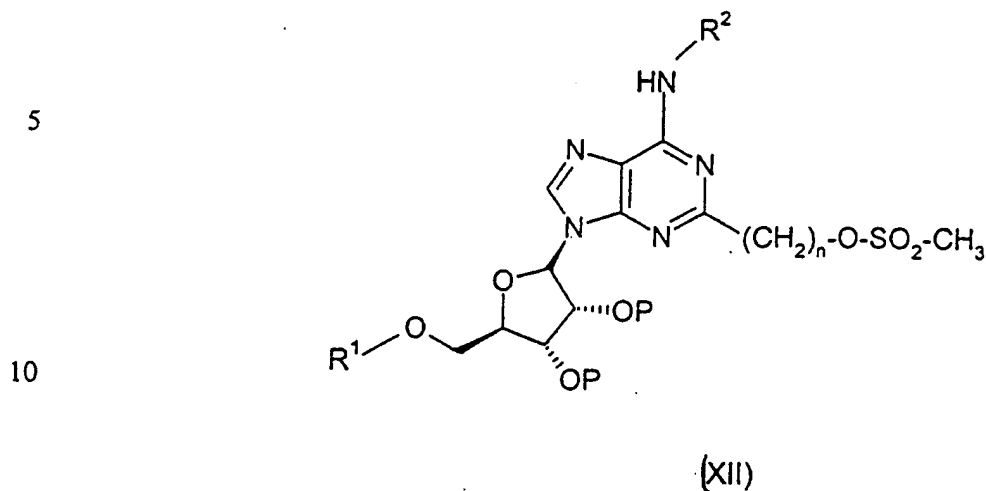
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Conversion of the  $-(CH_2)_nOH$  group of formula (IB) may take place by methods known to those skilled in the art. For example, standard methods may be used to prepare compounds of formula (I) wherein A is -OCONR<sup>a</sup> or -AR<sup>3</sup> is OR<sup>3</sup> wherein R<sup>3</sup> is not H from the corresponding compound of formula (IB).

30

A method to prepare compounds of formula (IIA) where q is 1, comprises reacting the corresponding compound of formula (IB) wherein n is 1 with

methanesulphonyl chloride in the presence of triethylamine to produce the corresponding methanesulphonate of formula (XII):



wherein n is 1, which can thereafter be reacted with an alkali metal cyanide to produce the compound of formula (IIA) wherein q is 1.

15

Alternatively, the methanesulphonate of formula (XII) wherein n is 1 or 2 (prepared similarly from a compound of the formula (IB) wherein n is 2) may be reacted with a compound of formula  $R^3A^2M$ , wherein  $A^2$  is O or S and M is a metal, such as sodium, to produce (after deprotection) the corresponding compound of formula (I) wherein A is O or S. The sulphide (i.e. wherein  $A=S$ ) may then be oxidised (as described below for the oxidation of the intermediate of formula (VI)) to the corresponding sulphone (wherein  $A=SO_2$ ). Alternatively, the unprotected methanesulphonate intermediate may be reacted with

20

25 a) a metal salt of a suitable sulphonamide to form a compound of the formula (I) wherein A is  $NR^aSO_2$ ,

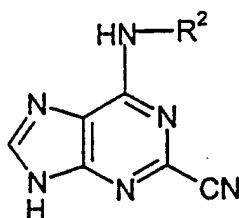
b) a suitable amine, optionally in the presence of a suitable acid acceptor (e.g. triethylamine or diisopropylethylamine), to form a compound of the formula (I) wherein A is  $NR^a$ ,

30 c) a suitable alkoxide to form a compound of the formula (I) wherein A is O, or

d) a suitable thiol in the presence of a suitable acid acceptor, e.g. triethylamine, to form a compound of the formula (I) wherein A is S.

A suitable method to prepare compounds of formula (I) wherein A is -NH but R<sup>3</sup> is other than H is by reductive amination, which comprises reaction of the corresponding compound of formula (IA) with a suitable aldehyde or ketone precursor for the group R<sup>3</sup> in the presence of a suitable reducing agent such as sodium triacetoxyborohydride, optionally in the presence of acetic acid, and in an inert solvent, such as THF or dichloromethane.

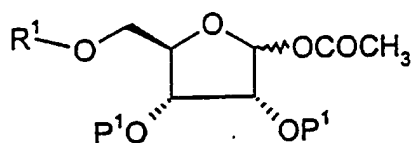
The compound of formula (IIA) wherein q is 0 (i.e. n is 1) may be prepared by reaction of the corresponding compound of formula (III):



(III)

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with a protected ester of formula (IV):



(IV)

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wherein P<sup>1</sup> is a protecting group, preferably -C(O)Ph.

Suitable de-protection, such as de-esterification, methods include (a) enzymatic de-esterification with an esterase; and (b) chemical de-esterification with a base, such as sodium methoxide, sodium carbonate or ammonia, in a suitable solvent, e.g. methanol or ethanol.

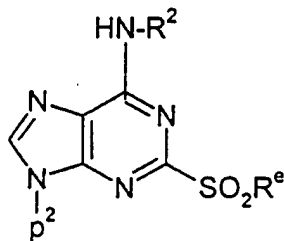
Alternative deprotection methods are well-known to those skilled in the art and include those described in "Protective Groups in Organic Synthesis" by Greene et al (Second Edition, Wiley-Interscience). In all the following methods,

30

appropriate protection and/or deprotection steps may be taken.

The compound of formula (III) may be prepared from the corresponding protected compound of formula (V):

5



10

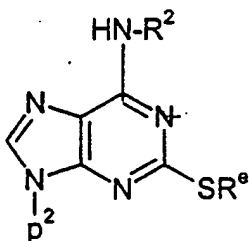
(V)

wherein P² is a protecting group, such as tetrahydropyranyl (THP) and Rᵉ is alkyl with a suitable cyanide derivative, such as an alkali metal cyanide such as KCN, followed by deprotection, such as with a mineral acid, *e.g.* aqueous HCl, in an alcoholic solvent, *e.g.* ethanol.

15

The compound of formula (V) may itself be prepared from the corresponding compound of formula (VI):

20



(VI)

25

wherein P² and Rᵉ are as defined in formula (V), by reaction with an oxidising agent, such as potassium peroxymonosulphate (OXONE (trade mark)).

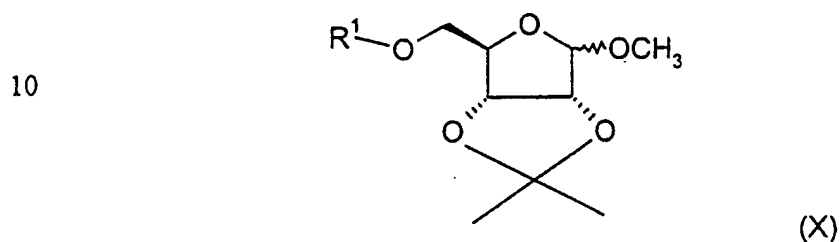
The compound of formula (VI) may itself be prepared from the corresponding halide of formula (VII):

30

(IX)

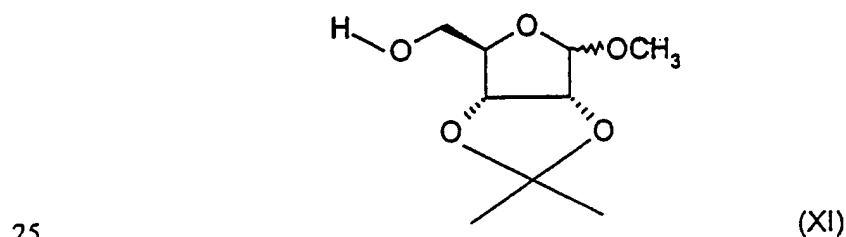
wherein P<sup>1</sup> is as defined in formula (IV), by standard methods, such as by  
 5 reaction with acetic acid/acetic anhydride in the presence of sulphuric acid.

The protected ether of formula (IX) may itself be prepared from the compound  
 of formula (X):



by reaction with an acid, e.g. aqueous HCl, in a polar solvent, e.g. methanol,  
 15 followed by protection of the reactive hydroxyl groups, as hereinbefore  
 described, such as by using benzoyl chloride in the presence of an acid  
 acceptor, e.g. pyridine.

The compound of formula (X) may be prepared from the corresponding alcohol  
 20 of formula (XI):



by standard methods, such as by the formation of an alkoxide ion by reaction  
 with sodium hydride, and then reaction with a compound of formula R<sup>1</sup>-X<sup>3</sup>  
 wherein X<sup>3</sup> is a leaving group such as halo, preferably iodo.

30 The compound of formula (XI) is obtainable from D-ribose as described in J.  
 Het. Chem., 13, 485 (1966).

All the compounds of the formula (I) may be prepared by deprotection of the corresponding compound (XIII) wherein the 3- and 4- hydroxy groups on the pendant tetrahydrofuran ring are suitably protected, e.g. by t-butyldimethylsilyl groups, under suitable conditions, e.g. using tetra-n-butylammonium fluoride in THF. Other suitable protecting groups and deprotection conditions are well-known to the skilled person such as from the Greene reference mentioned above.

Compounds of the formula (I) wherein A is  $C(O)NR^a$  may be prepared from the corresponding carboxylic acid (e.g. a compound of the formula (IIB)) by condensation with a suitable amine of the formula  $NHR^3R^a$ . Suitable condensation conditions include using N,N-dicyclohexylcarbodiimide, 1H-1,2,3-benzotriazol-1-ol monohydrate, diisopropylethylamine and dichloromethane.

Compounds of the formula (I) can also be interconverted using conventional functional group interconversion techniques.

All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the Examples and Preparations hereto.

A pharmaceutically acceptable salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

The anti-inflammatory properties of the compounds of the formula (I) are demonstrated by their ability to inhibit neutrophil function which indicates A2a

- receptor agonist activity. This is evaluated by determining the compound profile in an assay where superoxide production was measured from neutrophils activated by fMLP. Neutrophils were isolated from human peripheral blood using dextran sedimentation followed by centrifugation through Ficoll-Hypaque solution. Any contaminating erythrocytes in the granulocyte pellet were removed by lysis with ice-cold distilled water. Superoxide production from the neutrophils was induced by fMLP in the presence of a priming concentration of cytochalasin B. Adenosine deaminase was included in the assay to remove any endogenously produced adenosine that might suppress superoxide production.
- 10 The effect of the compound on the fMLP-induced response was monitored colorometrically from the reduction of cytochrome C within the assay buffer. The potency of the compounds was assessed by the concentration giving 50% inhibition ( $IC_{50}$ ) compared to the control response to fMLP.
- 15 The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.
- 20 For example, the compounds of the formula (I) can be administered orally, buccally or sublingually in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, sustained-, pulsed- or controlled-release applications.
- 25 Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia.
- 30 Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or a high molecular weight polyethylene glycol. For aqueous suspensions and/or elixirs, the compounds of the formula (I) may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol or glycerin, and combinations thereof.

The compounds of the formula (I) can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques. They are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) will usually be from 0.01 to 100 mg/kg, body weight of the subject to be treated, preferably from 0.1 to 100 mg/kg (in single or divided doses).

Thus tablets or capsules of the compound of the formula (I) may contain from 5 to 500 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.



The compounds of formula (I) can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser or nebuliser with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the formula (I) and a suitable powder base such as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 20 to 4000 µg of a compound of the formula (I) for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 20µg to 20mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

Alternatively, the compounds of the formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment, gel, suspension, dusting powder, spray or drug-incorporated dressing (e.g. a tulle dressing, a white soft paraffin or polyethylene glycol impregnated gauze dressing, or a hydrogel, hydrocolloid, alginate or film dressing). The compounds of the formula (I) may also be transdermally administered, for example, by the use of a skin patch.

For application topically to the skin, the compounds of the formula (I) can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following:

mineral oil, liquid petrolatum, white petrolatum, propylene glycol,

5 polyoxyethylene polyoxypropylene compound, emulsifying wax and water.

Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

10 They can also be formulated as a hydrogel with cellulose or polyacrylate derivatives or other viscosity modifiers.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

15

Thus the invention provides:-

- (i) a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;
- (ii) processes for the preparation of a compound of the formula (I) or a  
20 pharmaceutically acceptable salt or solvate thereof;
- (iii) a pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;
- (iv) a compound of the formula (I) or a pharmaceutically acceptable salt,  
25 solvate or composition thereof, for use as a medicament;
- (v) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament to treat a disease for which a A2a receptor agonist is indicated;
- 30 (vi) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of an anti-inflammatory agent;

- (vii) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of a respiratory disease;
- (viii) use as in (vii) where the disease is selected from the group consisting of  
5 adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis;
- (ix) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a  
10 medicament for the treatment of septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease,  
15 *Helicobacter pylori*-gastritis, non-*Helicobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing;
- (x) a method of treatment of a mammal, including a human being, to treat a disease for which a A2a receptor agonist is indicated including treating  
20 said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;
- (xi) a method of treatment of a mammal, including a human being, to treat an inflammatory disease including treating said mammal with an  
25 effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;
- (xii) a method of treatment of a mammal, including a human being, to treat a respiratory disease including treating said mammal with an effective  
amount of a compound of the formula (I) or with a pharmaceutically  
30 acceptable salt, solvate or composition thereof;
- (xiii) a method as in (xii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis,

- chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis;
- (xiv) a method of treatment of a mammal, including a human being, to treat septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Helicobacter pylori*-gastritis, non- *Helicobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing, including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof; and
- (xv) an intermediate of the formula (IIA), (IIB), (IB), (XII) or (XIII).

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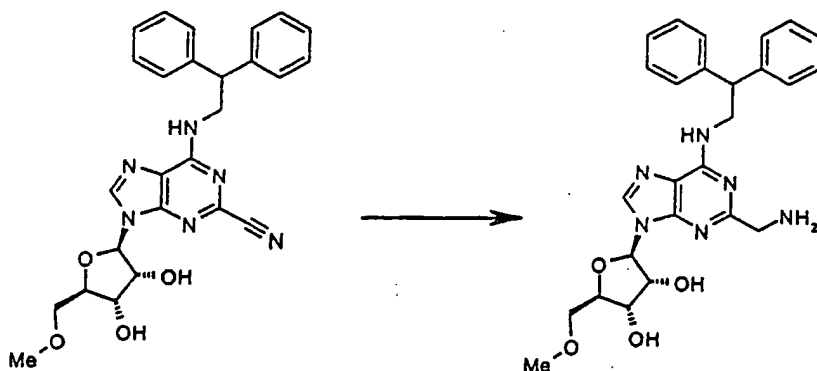
The following Examples illustrate the preparation of the compounds of the formula (I).

<sup>1</sup>H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts ( $\delta$ ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The mass spectra (m/z) were recorded in the thermospray ionisation mode. The following abbreviations have been used for common solvents: EtOAc, ethyl acetate; CH<sub>2</sub>Cl<sub>2</sub>, dichloromethane; CDCl<sub>3</sub>, deuteriochloroform; DMSO, dimethylsulphoxide. The abbreviation TBDMS means tert-butyldimethylsilyl and psi means pounds per square inch. Where thin layer chromatography has used it refers to silica gel TLC using silica gel 60 F<sub>254</sub> plates, R<sub>f</sub> is the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate.

30

## EXAMPLES

EXAMPLE 1: (2*R*,3*R*,4*S*,5*R*)-2-{2-(Aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol



A solution of 9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purine-2-carbonitrile (preparation 12) (2.15g, 4.42mmol) in ethanol (120ml) saturated with ammonia gas was treated with 5% palladium on charcoal (1g), pressurised to 1034 kPa (150psi) with hydrogen in a sealed vessel and stirred at room temperature for 24hr. The mixture was then filtered through Arbocel (trade mark) and the residue washed with ethanol. The solvent was removed under reduced pressure from the filtrate, the residue dissolved in ethanol and the solvent again removed under reduced pressure. A solid precipitated on re-evaporation which was then dissolved in hot ethanol (100ml) and the solution cooled and filtered. The residue was washed with ethanol then diethyl ether and dried to give the title compound as an off white solid (1.05g, 48%). The filtrate and washings were combined and the solvent removed under reduced pressure to give a residue which was then triturated with dichloromethane and a few drops of ethanol and filtered to afford a further portion of product (0.45g). MS: 491 (MH<sup>+</sup>).

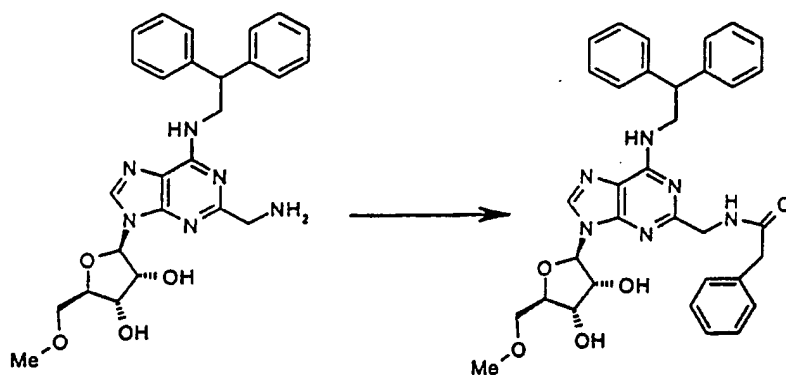
<sup>1</sup>H-NMR (d<sub>6</sub> DMSO) δ = 8.20 (1H, s), 7.70-7.60 (1H, br s), 7.40-7.20 (8H, m), 7.20-7.10 (2H, m), 5.95-5.80 (1H, m), 5.40 (1H, d), 5.20 (1H, d), 4.70-4.50 (2H,

m), 4.40-4.05 (2H, m), 4.05-3.95 (1H, m), 3.75 (1H, s), 3.60-3.40 (2H, m), 3.30 (3H, s), 1.95-1.80 (2H, br s).

Analysis : Found C, 63.16, H, 6.12, N, 16.99;  $C_{26}H_{30}N_6O_4 \cdot 0.25H_2O$  requires C, 63.08, H, 6.21, N, 16.98%.

5

**EXAMPLE 2: *N*-[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl]-2-phenylacetamide**



- 10 A stirred solution of (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (220mg, 0.45mmol) in dichloromethane (10ml) was treated with triethylamine (0.38ml, 2.70mmol) and phenylacetyl chloride (280mg, 1.80mmol) at 0°C and the resultant mixture stirred for 15min. The mixture was then stirred
- 15 at room temperature for 72hr. The solvent was removed under reduced pressure and methanol (20ml), saturated with ammonia gas, added. The resultant mixture was stirred at room temperature for 2hr, treated with 2 molar aqueous sodium hydroxide (10ml) and then left standing at room temperature for 24hr. The methanol was removed under reduced pressure and the aqueous
- 20 layer extracted with dichloromethane (x3). The combined organic layers were washed with water (x2), dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was dissolved in 1,4-dioxan (6ml), 0.88 aqueous ammonia solution (8ml) added and the mixture stirred at room temperature for 10 days. The 1,4-dioxan was removed under
- 25 reduced pressure and the aqueous layer extracted with dichloromethane (x3).

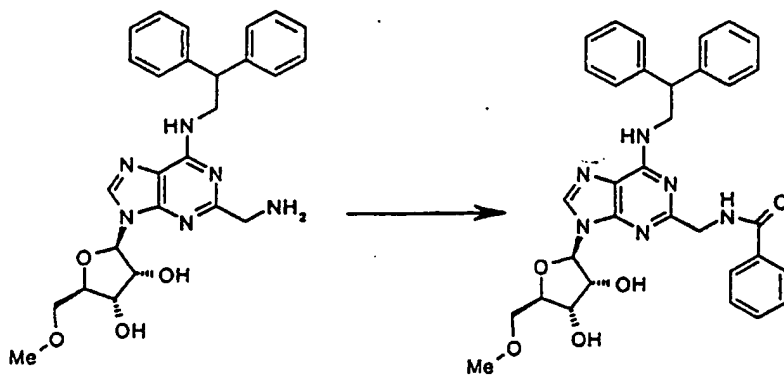
The combined organic extracts were dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol (97.5 : 2.5), to give the product which was  
 5 azeotroped with dichloromethane to afford the title compound as a foam (115mg). MS: 631 (MNa<sup>+</sup>).

<sup>1</sup>H-NMR (d<sub>6</sub> DMSO)  $\delta$  = 8.40-8.22 (1H, m), 8.22-8.10 (1H, m), 7.78-7.60 (1H, m), 7.40-7.0 (14H, m), 6.00-5.80 (1H, m), 5.50-5.40 (1H, m), 5.30-5.20 (1H, m),  
 10 4.70-4.42 (2H, m), 4.42-4.22 (2H, m), 4.22-3.90 (4H, m), 3.70-3.40 (4H, m), 3.40-3.10 (3H, m).

Analysis : Found C, 65.06, H, 5.79, N, 13.29; C<sub>34</sub>H<sub>36</sub>N<sub>6</sub>O<sub>6</sub> · 0.17CH<sub>2</sub>Cl<sub>2</sub> · 0.5H<sub>2</sub>O requires C, 64.96, H, 5.96, N, 13.30%.

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**EXAMPLE 3: *N*-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}benzamide**



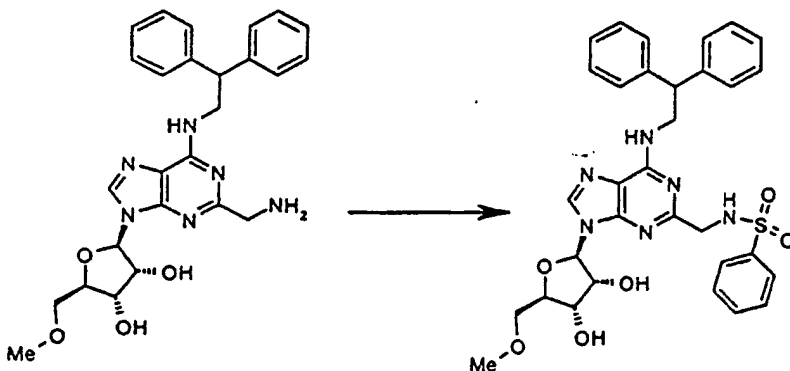
20 A stirred solution of (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (110mg, 0.22mmol) in dry tetrahydrofuran (20ml) was treated with triethylamine (0.1ml, 0.72mmol) and the mixture heated gently until all components had dissolved. The solution was then cooled to room temperature,  
 25 treated with a solution of benzoyl chloride (28mg, 0.20mmol) in dry

tetrahydrofuran (2ml) and the mixture stirred for 1.5hr. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol (95 : 5), to give the product which was then triturated with a mixture of diethyl ether and pentane, filtered off and dried to afford the title compound as a solid (80mg). MS: 595 (MH<sup>+</sup>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  = 7.95 (1H, s); 7.80 (2H, d), 7.60-7.50 (1H, br s), 7.45 (1H, m), 7.40-7.20 (12H, m), 5.95 (1H, d), 5.95-5.80 (1H, br s), 5.80-5.60 (1H, br s), 4.70 (2H, d), 4.55 (1H, t), 4.50-4.20 (4H, m), 3.70-3.50 (2H, m), 3.40-3.25 (3H, m).

Analysis : Found C, 66.06, H, 5.75, N, 13.97; C<sub>33</sub>H<sub>34</sub>N<sub>6</sub>O<sub>5</sub> · 0.25H<sub>2</sub>O requires C, 66.15, H, 5.80, N, 14.03%.

**EXAMPLE 4: *N*-[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}benzenesulfonamide**



The title compound was prepared by a similar method to example 3 from (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)-tetrahydro-3,4-furandiol (example 1) (110mg, 0.22mmol), benzenesulfonyl chloride (36mg, 0.20mmol) and triethylamine (0.1ml, 0.72mmol) to afford the title compound as a solid (100mg). MS: 631 (MH<sup>+</sup>).

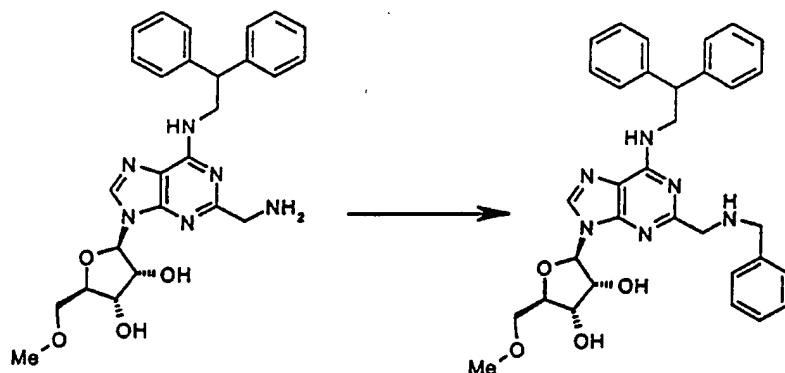


$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  = 7.90 (1H, s), 7.85 (2H, d), 7.45 (1H, m), 7.40-7.20 (12H, m), 5.90 (1H, d), 5.80-5.70 (2H, m), 5.95-5.85 (1H, br s), 4.50 (2H, m), 4.40-4.10 (6H, m), 3.65-3.55 (2H, m), 3.30 (3H, s), 3.00 (1H, s).

5 Analysis : Found C, 60.46, H, 5.44, N, 13.25;  $\text{C}_{32}\text{H}_{34}\text{N}_6\text{O}_6\text{S} \cdot 0.25\text{H}_2\text{O}$  requires C, 60.51, H, 5.47, N, 13.23%.

**EXAMPLE 5: (2R,3R,4S,5R)-2-[2-[(Benzylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol**

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(2R,3R,4S,5R)-2-[2-(Aminomethyl)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (110mg, 0.22mmol) was dissolved (using gentle heating) in dry tetrahydrofuran (15ml). The stirred solution was then cooled to room temperature and treated with a solution of benzaldehyde (21mg, 0.20mmol) in dry tetrahydrofuran (2ml) followed by addition of sodium triacetoxyborohydride (70mg, 0.33mmol). The resultant mixture was stirred at room temperature for 24hr, diluted with ethyl acetate and then washed sequentially with saturated aqueous sodium hydrogen carbonate and brine. The organic solution was then dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol (92 : 8) to afford the title compound as a solid

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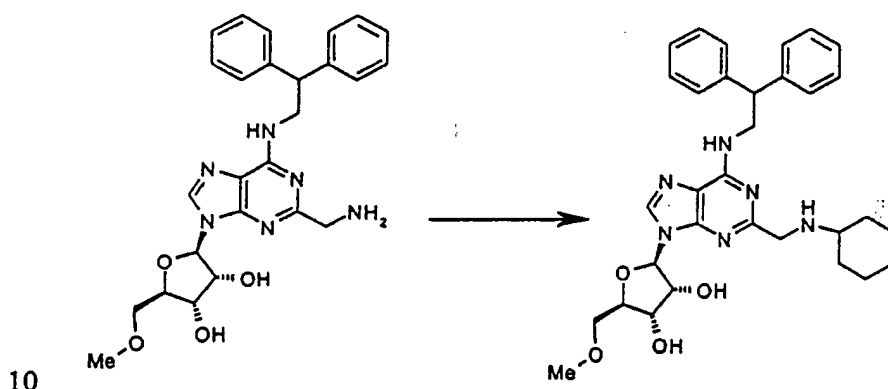
20

(67mg). MS: 581 ( $\text{MH}^+$ ).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  = 7.95 (1H, s), 7.40-7.20 (15H, m), 6.90 (1H, d), 5.90-5.70 (1H, br s), 4.40-4.20 (6H, m), 4.00-3.80 (4H, m), 3.65-3.55 (2H, m), 3.35 (3H, s).

Analysis : Found C, 67.43, H, 6.29, N, 14.29;  $\text{C}_{33}\text{H}_{36}\text{N}_6\text{O}_4 \cdot 0.5\text{H}_2\text{O}$  requires C, 67.22, H, 6.32, N, 14.25%.

**EXAMPLE 6: (2R,3R,4S,5R)-2-[2-[(Cyclohexylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol**

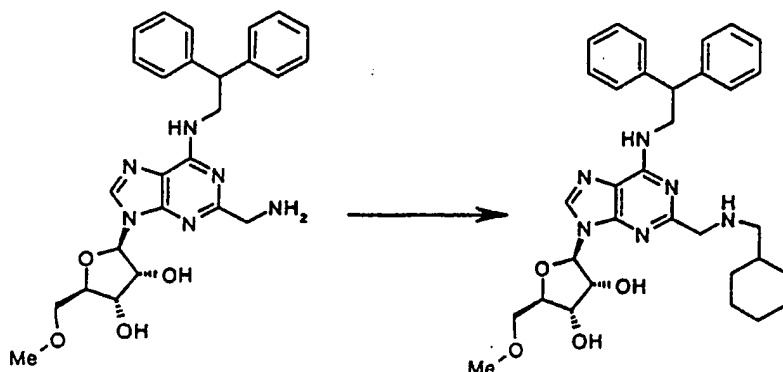


(2R,3R,4S,5R)-2-[2-(Aminomethyl)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (110mg, 0.22mmol) was dissolved (using gentle heating) in dry tetrahydrofuran (20ml) and the stirred solution treated with a solution of cyclohexanone (22mg, 0.22mmol) in dry tetrahydrofuran (2ml) followed by addition of sodium triacetoxyborohydride (70mg, 0.33mmol) and a solution of acetic acid (0.14ml, 0.25mmol) in dry tetrahydrofuran (2ml). The mixture was then stirred at room temperature for 24hr. The reaction mixture was diluted with diethyl ether, washed with saturated aqueous sodium hydrogen carbonate, brine, dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol : ammonia (95 : 5 : 0.5) changing to dichloromethane : methanol : ammonia (90 : 10 : 1) to afford the title compound as a solid (80mg). MS: 573 ( $\text{MH}^+$ ).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  = 7.90 (1H, s), 7.40-7.20 (10H, m), 5.90 (1H, d), 5.85-5.70 (1H, br s), 4.40-4.35 (4H, m), 4.35-4.20 (2H, m), 3.95 (2H, s), 3.65-3.55 (2H, m), 3.35 (3H, s), 2.60-2.45 (1H, m), 2.00-1.95 (2H, m), 1.80-1.70 (2H, m), 1.70-1.60 (1H, m), 1.30-1.10 (5H, m).

5 Analysis : Found C, 66.14, H, 7.08, N, 14.45;  $\text{C}_{32}\text{H}_{40}\text{N}_6\text{O}_4 \cdot 0.5\text{H}_2\text{O}$  requires C, 66.07, H, 7.10, N, 14.45%.

EXAMPLE 7: (2*R*,3*R*,4*S*,5*R*)-2-[2-[(Cyclohexylmethyl)amino]methyl]-6-  
 [(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-  
 3,4-furandiol

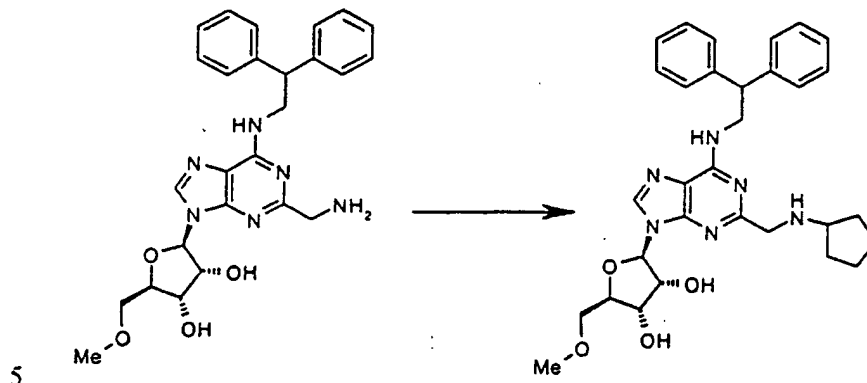


The title compound was prepared by a similar method to example 5 from (2*R*,3*R*,4*S*,5*R*)-2-[2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (110mg, 0.22mmol),  
 15 cyclohexanecarboxaldehyde (22mg, 0.20mmol) and sodium triacetoxymethylborohydride (70mg, 0.33mmol) to afford the title compound as a solid (55mg). MS: 587 ( $\text{MH}^+$ ).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  = 8.00 (1H, s), 7.40-7.20 (10H, m), 6.00 (1H, d), 5.90-5.70 (1H, br s), 4.50-4.40 (1H, m), 4.40-4.20 (5H, m), 4.10-3.90 (2H, m), 3.75-3.55 (2H, m), 3.35 (3H, s), 2.70-2.55 (2H, m), 1.90-1.75 (2H, m), 1.75-1.55 (4H, m), 1.40-1.05 (4H, m), 1.05-0.80 (2H, m).

Analysis : Found C, 65.40, H, 7.18, N, 13.62;  $\text{C}_{33}\text{H}_{42}\text{N}_6\text{O}_4 \cdot \text{H}_2\text{O}$  requires C, 65.54, H, 7.33, N, 13.90%.

**EXAMPLE 8: (2*R*,3*R*,4*S*,5*R*)-2-[2-[(Cyclopentylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol**



The title compound was prepared by a similar method to example 6 from (2*R*,3*R*,4*S*,5*R*)-2-[2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (110mg, 0.22mmol), cyclopentanone (18mg, 0.21mmol), sodium triacetoxymethylborohydride (70mg, 0.33mmol) and acetic acid (0.14ml, 0.25mmol) to afford the title compound as a solid (48mg). MS: 559 (MH<sup>+</sup>).

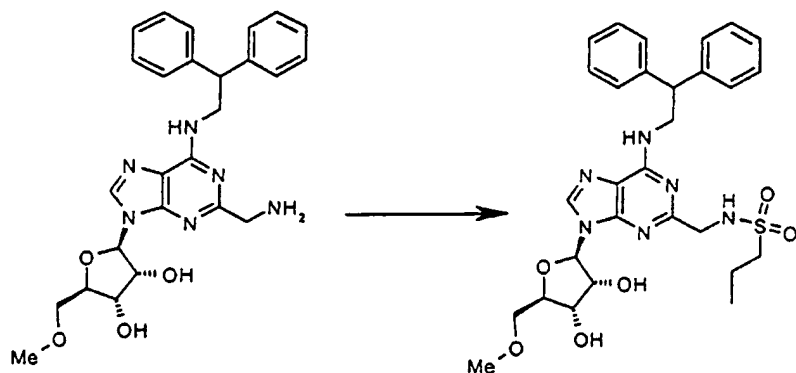
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<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 8.00 (1H, s), 7.40-7.20 (10H, m), 6.00 (1H, d), 5.85-5.70 (1H, br s), 4.50-4.40 (1H, m), 4.40-4.20 (5H, m), 4.20-3.95 (2H, m), 3.75-3.55 (2H, m), 3.45-3.40 (1H, br s), 3.35 (3H, s), 2.00-1.90 (2H, m), 1.90-1.65 (4H, m), 1.65-1.45 (2H, m), 1.25 (1H, s).

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**EXAMPLE 9: *N*-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}-1-propanesulfonamide**

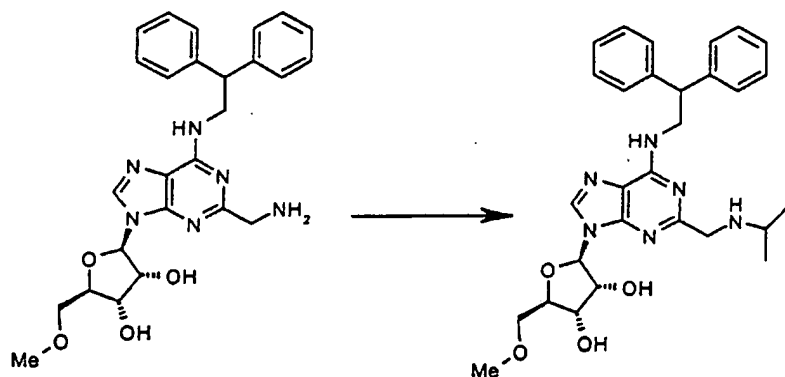
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The title compound was prepared by a similar method to example 3 from (2R,3R,4S,5R)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandi-ol (example 1) (110mg, 0.22mmol), 1-propanesulphonyl chloride (28mg, 0.19mmol) and triethylamine (0.1ml, 0.72mmol). The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol (98 : 2) gradually changing to dichloromethane : methanol (95 : 5) to afford the title compound as a solid (50mg). MS: 597 (MH<sup>+</sup>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 7.95 (1H, s), 7.40-7.20 (10H, m), 5.95 (1H, d), 5.90-5.80 (1H, br s), 5.50-5.40 (1H, m), 5.00-4.85 (1H, br s), 4.55 (2H, m), 4.40-4.20 (6H, m), 3.70-3.55 (2H, m), 3.35 (3H, s), 3.20-3.10 (1H, br s), 3.00 (2H, t), 1.95-1.80 (2H, m), 1.00 (3H, t).

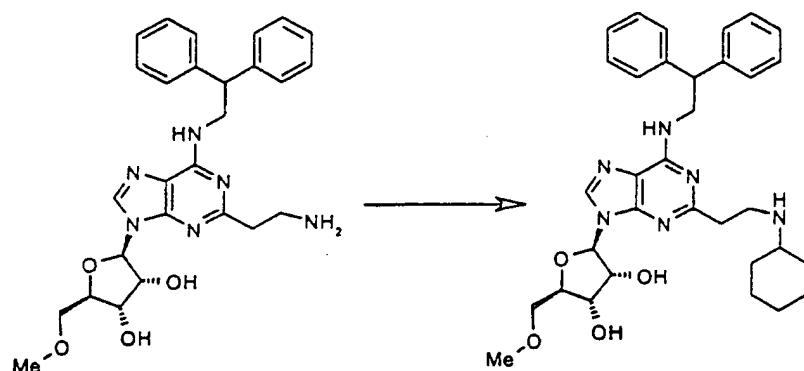
**EXAMPLE 10: (2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-Diphenylethyl)amino]-2-[(isopropylamino)methyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol**



- 5 The title compound was prepared by a similar method to example 6 from (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (100mg, 0.20mmol), acetone (12mg, 0.21mmol), sodium triacetoxymethylborohydride (70mg, 0.33mmol) and acetic acid (0.14ml, 0.25mmol) to afford the title compound (63mg). MS: 533 (MH<sup>+</sup>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 7.95 (1H, s), 7.35-7.20 (10H, m), 5.95 (1H, d), 5.90-5.70 (1H, br s), 4.40-4.30 (4H, m), 4.30-4.20 (2H, m), 3.90 (2H, s), 3.65-3.55 (2H, m), 3.30 (3H, s), 2.95-2.85 (1H, m), 1.20-1.10 (6H, m).

**EXAMPLE 12: (2R,3R,4S,5R)-2-{2-[2-(Cyclohexylamino)ethyl]-6-[(2,2-diphenyl ethyl)amino]-9H-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol**

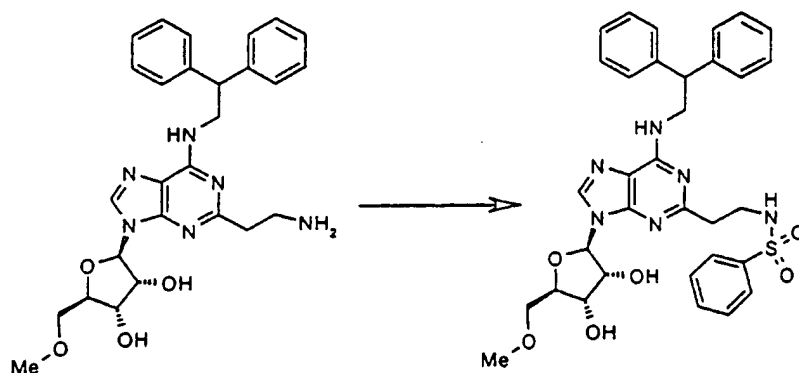


- 5 Sodium triacetoxyborohydride (75mg, 0.35mmol) and acetic acid (16mg, 0.27mmol) were added sequentially to a stirred solution of (2R,3R,4S,5R)-2-{2-(2-aminoethyl)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 11) (120mg, 0.24mmol) and cyclohexanone (23mg, 0.235mmol) in dichloromethane (15ml). The resulting
- 10 mixture was stirred at room temperature for 24hr, diluted with dichloromethane and washed sequentially with a saturated aqueous solution of sodium hydrogen carbonate, water and brine. The organic phase was dried with anhydrous sodium sulfate, the solvent removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a gradient system
- 15 of dichloromethane : methanol : ammonia (95 : 5 : 0.5) changing to dichloromethane : methanol : ammonia (90 : 10 : 1) to afford the title compound as a solid (78mg). MS: 587 (MH<sup>+</sup>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 7.92 (1H, s), 7.20-7.36 (10H, m), 5.91 (1H, d), 5.69 (1H, br s), 4.20-4.46 (6H, m), 3.57-3.68 (2H, m), 3.37 (3H, s), 3.10 (2H, br t), 2.99 (2H, br s), 2.51 (1H, m), 1.90 (2H, br s), 1.57-1.75 (3H, m), 1.05-1.29 (5H, m).

Analysis : Found C, 66.18, H, 7.25, N, 13.89; C<sub>33</sub>H<sub>42</sub>N<sub>6</sub>O<sub>4</sub>·0.75H<sub>2</sub>O requires C, 66.03, H, 7.30, N, 14.00%.

**EXAMPLE 13: *N*-(2-{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)ethyl)benzenesulfonamide**



5 The title compound was prepared by a similar method to example 3 using (2*R*,3*R*,4*S*,5*R*)-2-{2-(2-aminoethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 11) (200mg, 0.40mmol), benzenesulphonyl chloride (70mg, 0.40mmol) and triethylamine (0.15ml, 1.08mmol) to afford the title compound as a solid (145mg). MS: 645 (MH<sup>+</sup>).

10

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 7.91 (1H, s), 7.80 (2H, d), 7.20-7.55 (13H, m), 6.40 (1H, br t), 5.90 (1H, d), 5.74 (1H, br s), 4.20-4.50 (5H, m), 3.58-3.70 (2H, m), 3.32-3.45 (5H, m), 3.14 (1H, d), 2.92 (2H, br t).

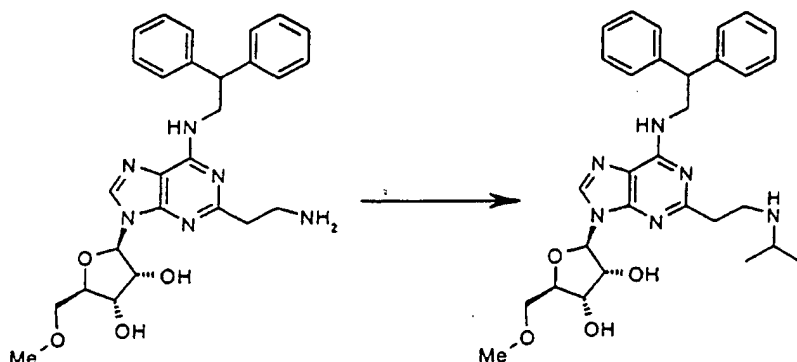
Analysis : Found C, 60.75, H, 5.64, N, 12.91; C<sub>33</sub>H<sub>36</sub>N<sub>6</sub>O<sub>6</sub>S. 0.25H<sub>2</sub>O requires C,

15

61.05, H, 5.67, N, 12.94%.

**EXAMPLE 14: (2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-diphenylethyl)amino]-2-[2-(isopropylamino)ethyl]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol**



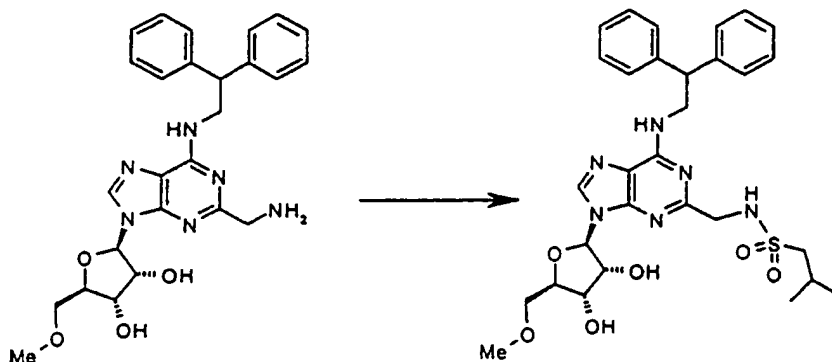


The title compound was prepared by a similar method to example 12 using (2*R*,3*R*,4*S*,5*R*)-2-{2-(2-aminoethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiyl (example 11) (120mg, 0.24mmol), acetone (14mg, 0.24mmol), acetic acid (16mg, 0.27mmol) and sodium triacetoxymethylborohydride (75mg, 0.35mmol) to afford the title compound as a solid (55mg). MS: 547 (MH<sup>+</sup>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 7.90(1H, s), 7.20-7.39 (10H, m), 5.90 (1H, d), 5.72 (1H, br s), 4.20-4.48 (5H, m), 3.55-3.66 (2H, m), 3.32 (3H, s), 2.80-3.10 (5H, m), 1.00-1.05 (6H, m)

Analysis : Found C, 64.66, H, 7.05, N, 15.00; C<sub>30</sub>H<sub>38</sub>N<sub>6</sub>O<sub>4</sub> · 0.5H<sub>2</sub>O requires C, 64.85, H, 7.07, N, 15.12%.

**EXAMPLE 15: *N*-{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl}-2-methyl-1-propanesulfonamide**

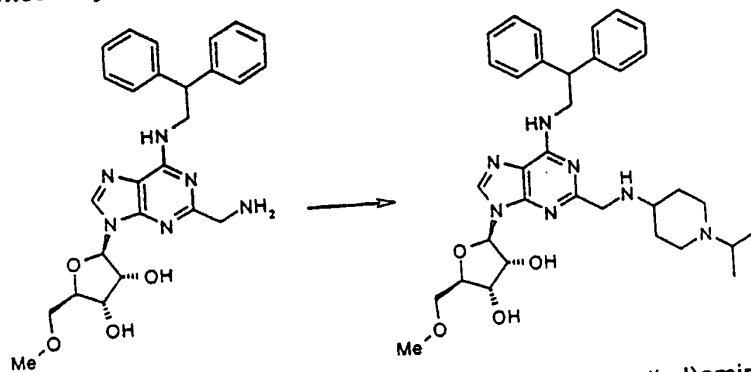


(2*R*,3*R*,4*S*,5*R*)-2-{2-(Aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (300mg, 0.61mmol) was dissolved in dry tetrahydrofuran (20ml) (using gentle heating), a solution of 2-methyl-1-propanesulphonyl chloride (50mg, 0.32mmol) in dry tetrahydrofuran (2.5ml) added and the mixture stirred at room temperature for 18hr under a nitrogen atmosphere. A solution of triethylamine (100mg, 0.98mmol) and 2-methyl-1-propanesulphonyl chloride (50mg, 0.32mmol) in dry tetrahydrofuran (5ml) was added and the resulting mixture stirred for a further 5hr. The solvent was then removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol (97 : 3), to give the product as a foam (117mg). MS: 611 (MH<sup>+</sup>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 7.96 (1H, s), 7.20-7.40 (10H, m), 5.95 (1H, d), 5.50 (1H, t), 5.03 (1H, br s), 4.55 (2H, s), 4.20-4.42 (6H, m), 3.56-3.70 (2H, m), 3.38 (3H, s), 2.96 (2H, d), 2.20-2.35 (1H, m), 1.08 (6H, d).

Analysis : Found C, 58.22, H, 6.29, N, 13.45; C<sub>30</sub>H<sub>38</sub>N<sub>6</sub>O<sub>6</sub>S.0.1CH<sub>2</sub>Cl<sub>2</sub> requires C, 58.38, H, 6.22, N, 13.57%.

20 **EXAMPLE 16:** (2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-Diphenylethyl)amino]-2-[(1-isopropyl-4-piperidiny)amino]methyl}-9*H*-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol-

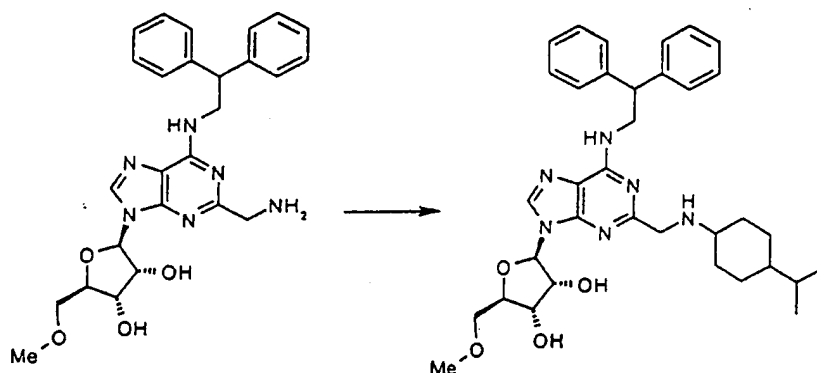


25 (2*R*,3*R*,4*S*,5*R*)-2-{2-(Aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (310mg, 0.63mmol) was

dissolved (using gentle heating) in dry tetrahydrofuran (20ml). The resulting solution was cooled to room temperature and, with stirring, treated with a solution of 1-isopropyl-4-piperidinone (90mg, 0.63mmol) and acetic acid (45mg) in dry tetrahydrofuran (5ml). The mixture was stirred for 1hr, sodium triacetoxymethylborohydride (200mg, 0.94mmol) added and stirring continued for a further 18hr. The solvent was then removed under reduced pressure and the residue partitioned between a saturated aqueous solution of sodium hydrogen carbonate and ethyl acetate. The organic phase was separated and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol : ammonia (90 : 10 : 0.5) changing to dichloromethane : methanol : ammonia (85 : 15 : 0.75) to afford the title compound as a foam (140mg). MS: 616 (MH<sup>+</sup>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  = 7.90 (1H, s), 7.19-7.38 (10H, m), 5.94 (1H, d), 5.81 (1H, br s), 4.21-4.44 (6H, m), 3.88 (2H, s), 3.53-3.70 (2H, m), 3.36 (3H, s), 2.70-2.90 (3H, m), 2.57 (1H, m), 2.20 (4H, t), 1.94 (3H, br d), 1.52 (2H, m), 1.06 (6H, d).  
Analysis : Found C, 62.93, H, 7.48, N, 14.95; C<sub>34</sub>H<sub>45</sub>N<sub>7</sub>O<sub>4</sub>.H<sub>2</sub>O.0.16CH<sub>2</sub>Cl<sub>2</sub> requires C, 63.33, H, 7.36, N, 15.13%.

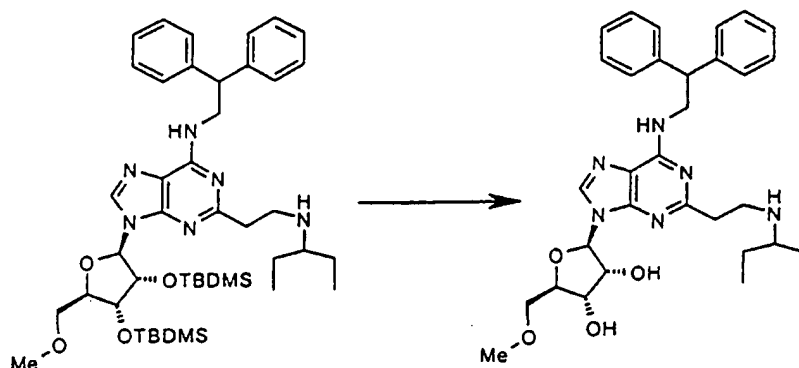
**EXAMPLE 17:** *Cis*-(2*R*,3*R*,4*S*,5*R*)-2-(6-[(2,2-diphenylethyl)amino]-2-[(4-isopropylcyclohexyl)amino]methyl)-9*H*-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol and *trans*-(2*R*,3*R*,4*S*,5*R*)-2-(6-[(2,2-diphenylethyl)amino]-2-[(4-isopropylcyclohexyl)amino]methyl)-9*H*-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol



(2R,3R,4S,5R)-2-{2-(Aminomethyl)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (300mg, 0.61mmol) was dissolved (using gentle heating) in dry tetrahydrofuran (20ml). The resulting solution was cooled to room temperature and, with stirring, treated with a solution of 4-isopropylcyclohexanone (85mg, 0.61mmol) and acetic acid (44mg) in dry tetrahydrofuran (5ml), followed by addition of solid sodium triacetoxyborohydride (194mg, 0.91mmol). The resulting mixture was then stirred at room temperature for 18hr before removal of the solvent under reduced pressure and partitioning of the residue between a saturated aqueous solution of sodium hydrogen carbonate and ethyl acetate. The organic phase was separated and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (94 : 6 : 0.3) to afford the title compound as a foam and as a mixture of *cis* and *trans* isomers (170mg). MS: 615 (MH<sup>+</sup>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 7.89 (1H, s), 7.18-7.38 (10H, m), 5.84-5.97 (2H, m), 4.20-4.42 (6H, m), 3.89 (2H, d), 3.50-3.70 (2H, m), 3.31 (1H, s), 2.80 (1H, br s), 2.48 (1H, br t), 2.00 (1H, br t), 0.98-1.79 (9H, m), 0.84 (6H, d).

**EXAMPLE 18 :** (2R,3R,4S,5R)-2-(6-[(2,2-Diphenylethyl)amino]-2-[(1-ethylpropyl)amino]ethyl)-9H-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol



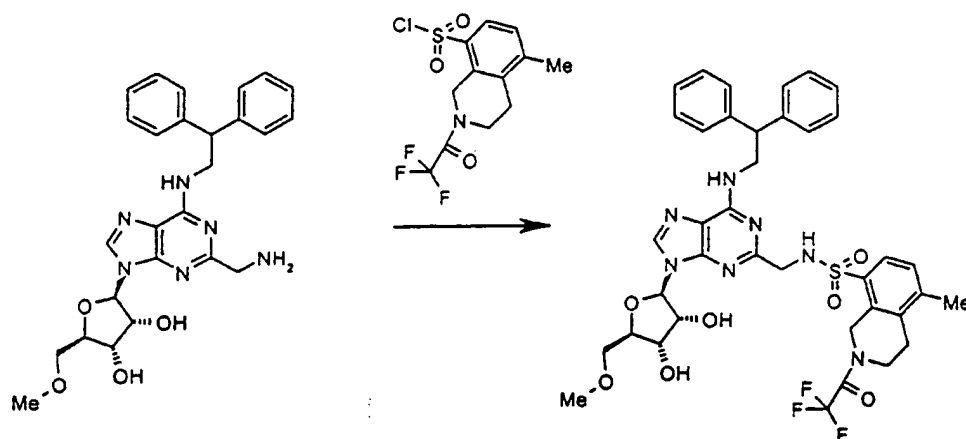
N-(2-{9-[(2R,3R,4R,5R)-3,4-bis[[*tert*-butyl(dimethyl)silyl]oxy]-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9H-purin-2-yl}ethyl)-N-(1-ethylpropyl)amine (250mg, 0.31mmol) (preparation 19) was dissolved in dry tetrahydrofuran (1ml), a 1M solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1ml, 1mmol) added and the mixture stirred at room temperature for 3 days. The solvent was removed under reduced pressure and the residue purified by column chromatography eluting with a gradient system of dichloromethane : methanol : ammonia (94 : 6 : 0.6) changing to dichloromethane : methanol : ammonia (90 : 10 : 1) to give the crude product as a foam. This was dissolved in ethyl acetate (15ml) and the solution washed sequentially with dilute aqueous sodium hydroxide solution, brine and water, then dried with anhydrous sodium sulfate. The solvent removed under reduced pressure to give the title compound as a powder (100mg). MS: 575 (MH<sup>+</sup>)

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  = 7.85 (1H, s), 7.18-7.36 (10H, m), 5.92 (1H, d), 5.70 (1H, br s), 4.20-4.48 (6H, m), 3.55-3.67 (2H, m), 3.33 (3H, s), 3.00-3.20 (4H, m), 2.52 (1H, br t), 1.43-1.54 (4H, m), 0.85-0.92 (6H, m).

Analysis : Found C, 64.77, H, 7.32, N, 14.03; C<sub>32</sub>H<sub>42</sub>N<sub>6</sub>O<sub>4</sub>·H<sub>2</sub>O requires C, 64.84, H, 7.48, N, 14.18 %

**EXAMPLE 19 : N-({9-[2R,3R,4S,5R]-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9H-**

purin-2-yl)methyl)-5-methyl-2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydro-8-isoquinolinesulfonamide.



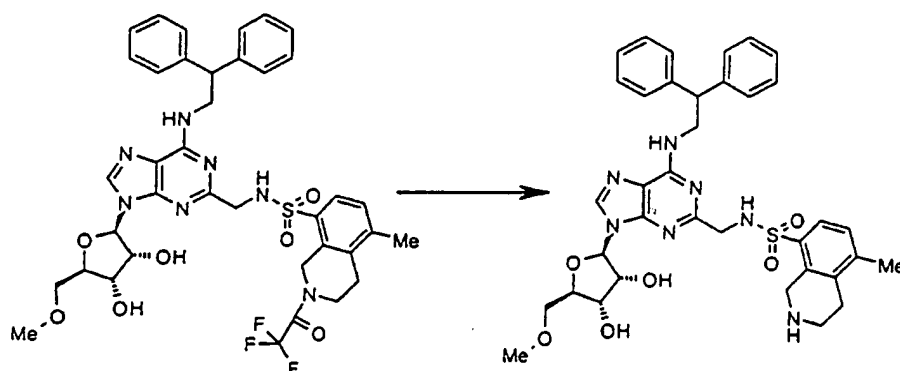
- 5 The title compound was prepared by a similar method to example 3 using (2*R*,3*R*,4*S*,5*R*)-2-{2-(Aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (240mg, 0.49mmol), 5-methyl-2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydro-8-isoquinolinesulfonyl chloride (prepared as described in WO-95/13274) (140mg, 0.41mmol) and triethylamine (150mg, 0.15ml) to give title compound (340mg) as a solid.  $R_f$  0.65 in
- 10 dichloromethane : methanol : ammonia (80 : 20 : 1)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 8.00 (1H, s), 7.95-7.90 (1H, m), 7.35-7.20 (12H, m), 6.30-6.20 (1H, m), 6.05-6.00 (1H, m), 5.80-5.75 (1H, m), 5.40-5.30 (1H, m), 5.25-5.15 (1H, m), 4.60-4.50 (2H, m), 4.40-4.05 (6H, m), 4.00-3.80 (2H, m), 3.80-3.60 (2H, m), 3.40 (3H, s), 3.30-3.20 (1H, m), 2.90-2.80 (2H, m), 2.30 (3H, s).

15

**EXAMPLE 20 : N-{[9-[2*R*,3*R*,4*S*,5*R*]-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]}-5-methyl-1,2,3,4-tetrahydro-8-isoquinolinesulfonamide.**

20



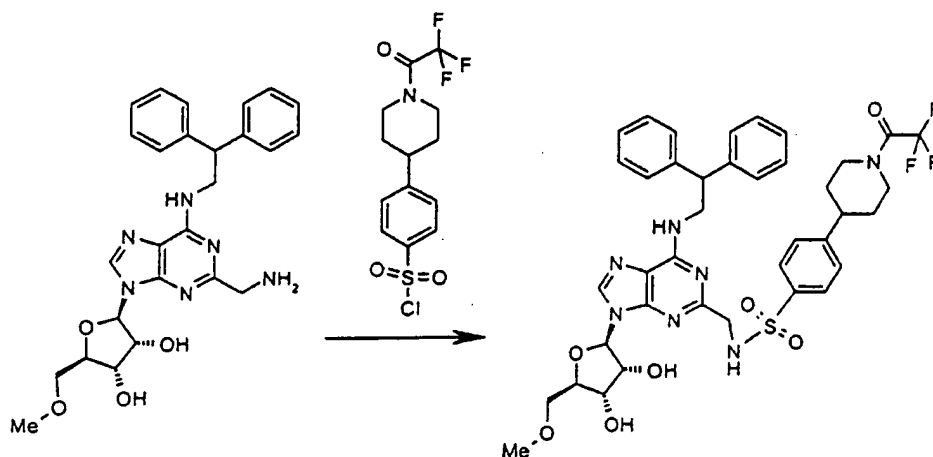
N-((9-([2R,3R,4S,5R]-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-  
 [(2,2-diphenylethyl)amino]-9H-purin-2-yl)methyl)-5-methyl-2-(2,2,2-  
 trifluoroacetyl)-1,2,3,4-tetrahydro-8-isoquinolinesulfonamide (example 19)

(290mg, 0.36mmol) was dissolved in a saturated methanolic solution of  
 ammonia (20ml) and the solution stirred for 24hr. The solvent was then  
 removed under reduced pressure and the residue dissolved in ethyl acetate  
 (25ml) to give a solution which was then washed with water (2 x 10ml) followed  
 by brine (10ml). The solvent was removed under reduced pressure and the  
 residue triturated with diethyl ether and dried. This gave the title compound  
 (179mg) as a solid. MS: 701 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.15 (1H, s), 7.85 (1H, d), 7.5-7.15 (10H, m), 7.1 (1H, d),  
 6.05 (1H, s), 5.80 (1H, br s), 4.80-4.60 (2H, m), 4.50-4.40 (1H, m), 4.35-4.05  
 (7H, m), 3.85-3.75 (1H, m), 3.70-3.60 (1H, m), 3.45 (3H, s), 3.25-3.15 (1H, m),  
 2.95-2.85 (1H, m), 2.70-2.60 (2H, m), 2.20 (3H, s).

Analysis : Found C, 58.96, H, 5.74, N, 13.54; C<sub>36</sub>H<sub>41</sub>N<sub>7</sub>O<sub>6</sub>S.2H<sub>2</sub>O requires C,  
 58.77, H, 6.17, N, 13.33%

**EXAMPLE 21:** N-((9-([2R,3R,4S,5R]-3,4-dihydroxy-5-  
 (methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9H-  
 purin-2-yl)methyl)-4-[1-(2,2,2-trifluoroacetyl)-4-  
 piperidinyl]benzenesulfonamide.

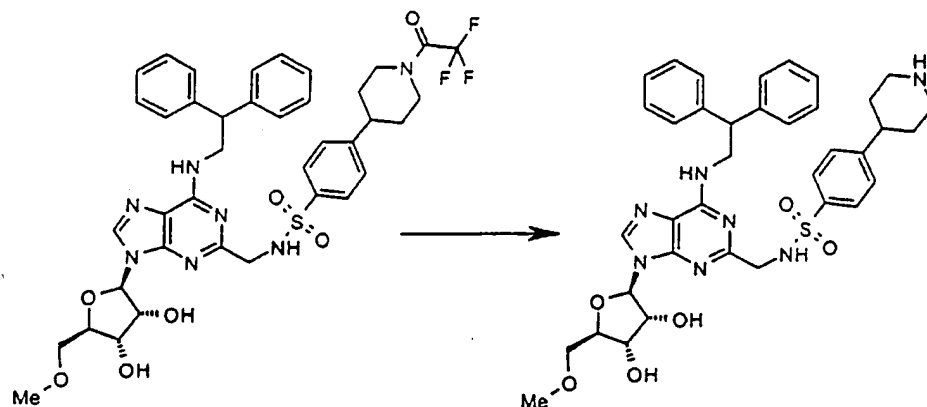


The title compound was prepared by a similar method to example 3 using (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (250mg, 0.51mmol), 4-  
 5 [1-(2,2,2-trifluoroacetyl)-4-piperidiny]benzenesulfonyl chloride (preparation 20) (157mg, 0.48mmol) and triethylamine (155mg, 1.53mmol) in tetrahydrofuran (25ml). This gave the title compound as a solid (300mg). MS: 811 (MH<sup>+</sup>)

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.80-7.75 (2H, m), 7.40-7.10 (12H, m), 5.90-  
 10 5.85 (1H, m), 5.85-5.75 (2H, m), 4.90 (1H, br s), 4.70-4.60 (1H, m), 4.50 (2H, s), 4.35-4.05 (6H, m), 3.70-3.55 (2H, m), 3.35 (3H, s), 3.25-3.10 (2H, m), 2.85-2.70 (2H, m), 1.90-1.80 (2H, m), 1.70-1.45 (2H partially obscured by H<sub>2</sub>O).

**EXAMPLE 22:** *N*-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}-4-(4-piperidiny)benzenesulfonamide  
 15

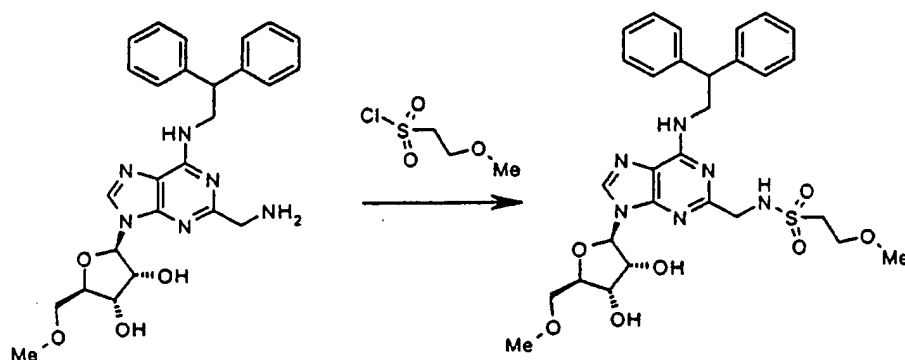




The title compound was prepared by a similar method to example 20 using *N*-  
 ((9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-  
 [(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl)-4-[1-(2,2,2-trifluoroacetyl)-4-  
 5 piperidiny]benzenesulfonamide (0.26g, 0.32mmol) (example 21) and a  
 saturated methanolic solution of ammonia (20ml). This gave the title compound  
 (180 mg) as a solid. MS: 715 (MH<sup>+</sup>)

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.95 (1H, s), 7.75-7.5 (2H, m), 7.35-7.20 (10H, m), 7.15-  
 10 7.05 (2H, m), 5.90-5.75 (2H, m), 4.50-4.40 (2H, m), 4.35-4.10 (7H, m), 3.70-  
 3.55 (2H, m), 3.35 (3H, s), 3.20-3.05 (2H, m), 2.70-2.60 (2H, m), 2.60-2.45 (1H,  
 m) 1.75-1.25 (4H, m).

**EXAMPLE 23:** *N*-{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-  
 15 (methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-  
 purin-2-yl)methyl}-2-methoxy-1-ethanesulfonamide.

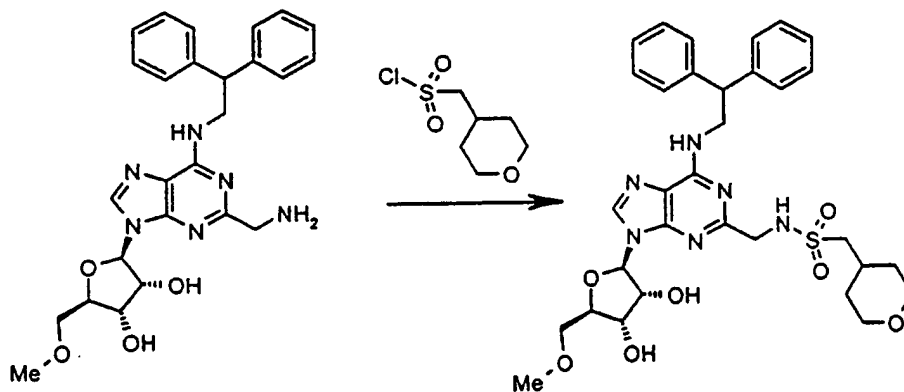


The title compound was prepared by a similar method to example 3 using (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (250mg, 0.49mmol), 2-methoxy-1-ethanesulfonyl chloride (J. Org. Chem. 2633, 26, 1961) (77mg, 0.49mmol), triethylamine (150mg, 1.5mmol) in tetrahydrofuran (23ml). The crude product was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (96 : 4 : 0.2) gave the title compound (225mg) as an oil. MS: 614 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.95 (1H, s), 7.35-2.20 (10H, m), 6.00-5.95 (1H, m), 5.90-5.75 (1H, m), 5.55-5.50 (1H, m), 5.10 (1H, br s), 4.50 (2H, s), 4.40-4.20 (6H, m), 3.85-3.75 (2H, m), 3.45-3.35 (5H, m), 3.30 (3H, s), 3.05 (1H, s).

Analysis : Found C, 55.92, H, 5.80, N, 13.42; C<sub>29</sub>H<sub>38</sub>N<sub>6</sub>O<sub>7</sub>S.0.167CH<sub>2</sub>Cl<sub>2</sub> requires C, 55.89, H, 5.84, N, 13.41%

**EXAMPLE 24:** *N*-{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl}(tetrahydro-2*H*-pyran-4-yl)methanesulfonamide.



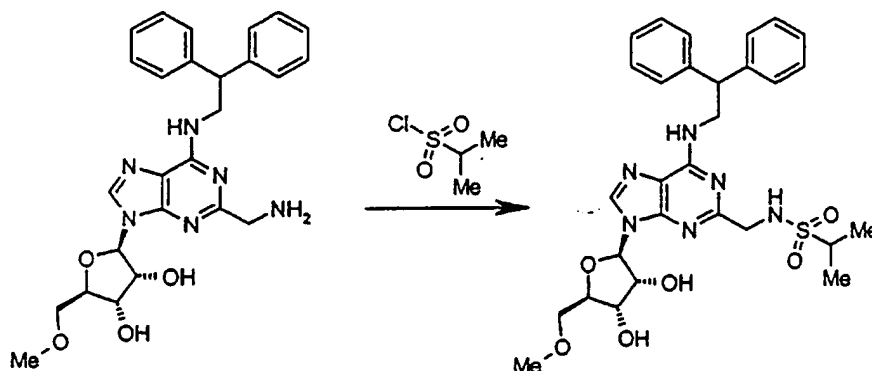
The title compound was prepared by a similar method to example 3 using (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-

5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (245mg, 0.48mmol), tetrahydro-2H-pyran-4-ylmethanesulfonyl chloride (preparation 21) (95mg, 0.48mmol), triethylamine (145mg, 1.44mmol) in tetrahydrofuran (23ml).

Purification by column chromatography on silica gel eluting with a solvent  
 5 system of dichloromethane : methanol : ammonia (95 : 5 : 0.25) gave the title compound as an oil (118mg). MS: 654 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 7.90 (1H, s), 7.35-7.20 (10H, m), 5.95-5.90 (1H, m), 5.90-5.75 (1H, br s), 5.50-5.45 (1H, m), 4.90-4.80 (1H, br s), 4.60-4.50 (2H, m), 4.40-  
 10 4.20 (6H, m), 3.95-3.90 (2H, m), 3.70-3.55 (2H, m), 3.45-3.30 (5H, m), 3.10 (1H, br s), 3.05-2.95 (2H, m), 2.30-2.15 (1H, m), 1.85-1.75 (2H, m), 1.50-1.30 (2H, m).

**EXAMPLE 25: N-{9-[(2R,3R,4S,5R)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9H-purin-2-yl}methyl)-2-propanesulfonamide.**  
 15

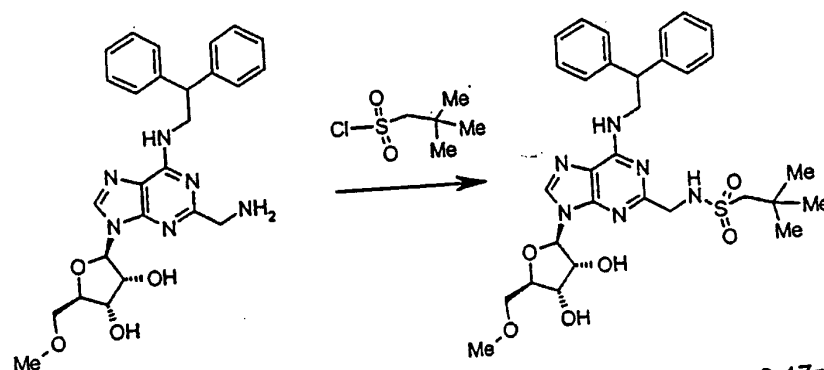


Isopropylsulphonyl chloride (120mg, 0.84mmol) was added to a stirred solution  
 20 of (2R,3R,4S,5R)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (408mg, 0.8mmol) (example 1) in 2,6-lutidine (10ml). The mixture was stirred at room temperature for 24hr followed by stirring at 50°C for a further 5 days. A second portion of isopropylsulphonyl chloride (120mg, 0.84mmol) and lutidine (4ml) were added  
 25 and the reaction stirred at 50°C for 24hr. A third portion of isopropylsulphonyl

chloride (120 mg, 0.84mmol) was added and heating at 50°C continued for a further 24hr. At the end of this period the solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and aqueous ammonia. The organic phase was separated and the solvent removed under reduced pressure to give a residue which was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (98 : 2 : 0.1) increasing to dichloromethane : methanol : ammonia (96 : 4 : 0.2). This gave the title compound (118mg) as an oil. MS: 597 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) mixture of rotamers  $\delta$  = 7.90 (1H, s), 7.35-7.20 (10H, m), 5.95-5.90 (1H, m), 5.85-5.70 (1H, br s), 4.90 (1H, br s), 4.60-4.15 (8H, m), 3.70-3.55 (2H, m), 3.30 (3H, s), 3.25-3.10 (2H, m), 1.80 (1H, d), 1.40 (5H, d).

**EXAMPLE 26:** *N*-{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl}-2,2-dimethyl-1-propanesulfonamide.



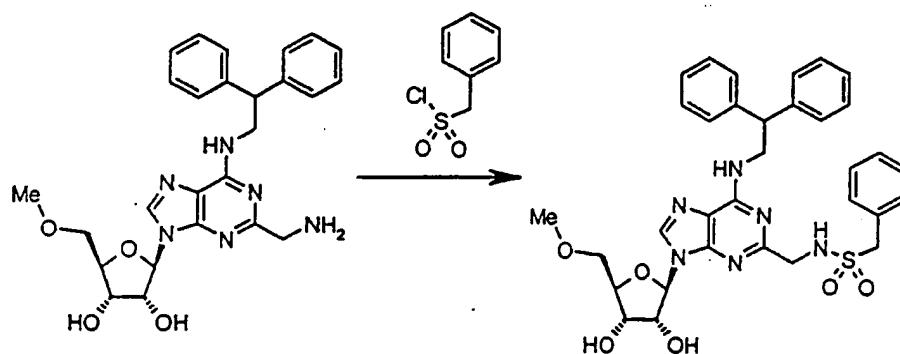
A solution of 2,2-dimethyl-1-propanesulfonyl chloride (80 mg, 0.47mmol) (Synthesis 489, *Z.* 1974) in tetrahydrofuran (5ml) was added to a stirred solution of (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (450 mg, 0.92mmol) in tetrahydrofuran (30ml) and the mixture stirred for 24hr at room temperature. The solvent was then removed under reduced pressure and the

residue partitioned between ethyl acetate and aqueous ammonia. The organic phase was separated and the solvent removed under reduced pressure to give a residue which was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol (19 : 1) to give title compound (40 mg) as an oil. MS: 625 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.95 (1H, s), 7.35-7.15 (10H, m), 6.00-5.95 (2H, m), 5.60-5.55 (1H, m), 5.10 (1H, br s), 4.55-4.45 (2H, m), 4.40-4.20 (6H, m), 3.70-3.55 (2H, m), 3.4 (1H, br s), 3.35 (3H, s), 3.00 (2H, s), 1.15 (9H, s).

10

**EXAMPLE 27: *N*-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}(phenyl)methanesulfonamide.**



15

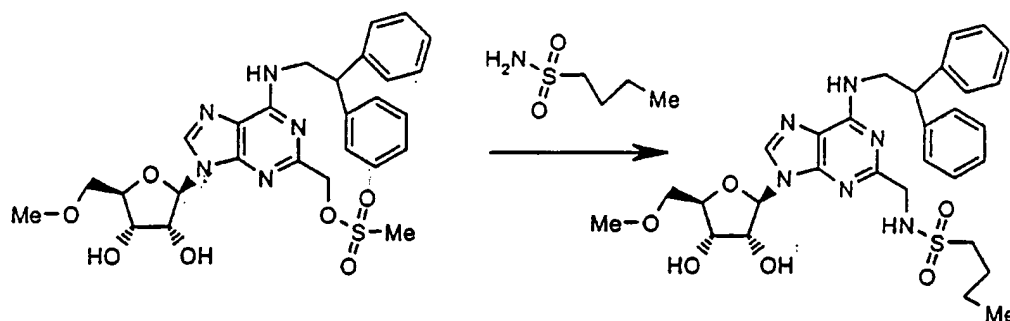
The title compound was prepared by a similar method to example 3 using (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (265mg, 0.54mmol), phenylmethanesulfonyl chloride (98mg, 0.51mmol) and triethylamine (185mg, 1.83mmol) in dry tetrahydrofuran (23ml). This gave the title compound (240mg) as a gum. MS: 645 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, br s), 7.40-7.20 (15H, m), 5.90-5.80 (2H, m), 5.50-5.45 (1H, m), 4.90 (1H, br s), 4.55-4.45 (2H, m), 4.35-4.10 (8H, m), 3.65-3.50 (2H, m), 3.30 (3H, s), 3.15 (1H, s).

25

Analysis : Found C, 60.09, H, 5.63, N, 12.24;  $C_{33}H_{36}N_6O_6S \cdot 0.5H_2O \cdot 0.1CH_2Cl_2$  requires C, 60.04, H, 5.66, N, 12.69%.

5 **EXAMPLE 28:** *N*-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl}-1-butanesulfonamide.

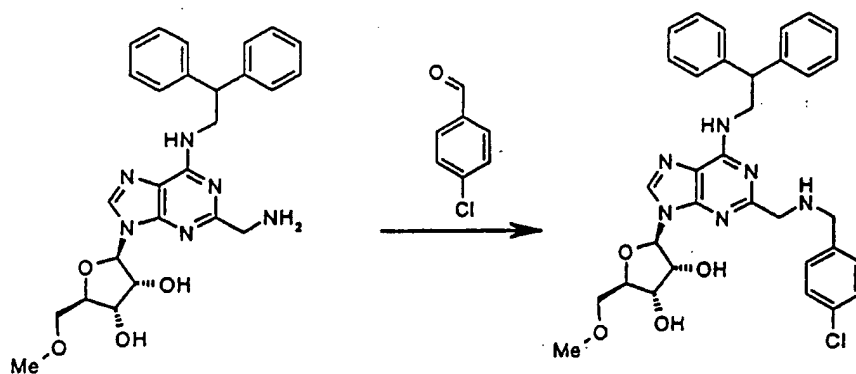


10

1-Butanesulphonamide (J. Am. Chem. Soc. 5512, 72, 1950) (280mg, 2.1mmol) was dissolved in stirred tetrahydrofuran (10ml) and sodium hydride added (0.05g of 80% dispersion in mineral oil, 1.56mmol). After effervescence had ceased the reaction mixture was cooled to 0°C and a solution of {9-  
 15 [(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl} methanesulfonate (300mg, 0.52mmol) (preparation 25) in tetrahydrofuran (5ml) added. The reaction mixture was stirred for 24hr then quenched by the addition of methanol (0.5ml). The solvent was removed under reduced pressure and the residue partitioned  
 20 between water (50ml) and dichloromethane (100ml). The organic layer was separated and dried with anhydrous magnesium sulfate. The residue after solvent evaporation under reduced pressure was purified by column chromatography on silica gel eluting with a solvent system of ethyl acetate : hexane (1 : 1) followed by ethyl acetate followed by dichloromethane :  
 25 methanol (19 : 1). This gave the title compound (60mg) as a foam. MS: 612 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) Mixture of rotamers δ = 8.00 (0.3H, br s), 7.95 (0.7H, br s), 7.40-7.20 (10H, m), 5.95-5.90 (1H, m), 4.75-4.65 (2H, m), 4.55-4.20 (6H, m), 3.70-3.55 (2H, m), 3.35 (3H, s), 3.15 (0.6H, s), 3.10-3.00 (1.4H, m), 1.85-1.75 (1.4H, m), 1.60-1.55 (0.6H, m obscured by HOD), 1.50-1.35 (1.4H, m), 1.25 (0.6H, s), 0.95-0.85 (3H, m).

**EXAMPLE 29: (2*R*,3*R*,4*S*,5*R*)-2-{2-[[4-Chlorobenzyl]amino]methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol.**

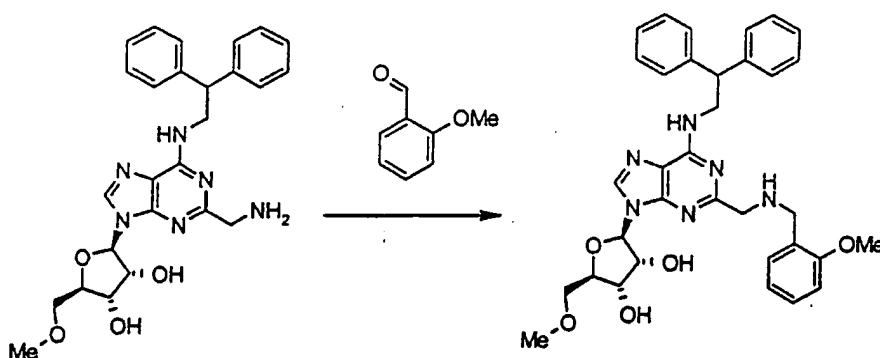


The title compound was prepared by a similar method to example 5 using (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (200mg, 0.4mmol), sodium triacetoxyborohydride (152mg, 0.72mmol) and 4-chlorobenzaldehyde (75mg, 0.53mmol). The product was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol (98 : 2) gradually increasing polarity to dichloromethane : methanol (90 : 10), which gave the title compound (53 mg) as a foam. MS: 615 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.35-7.20 (14H, m), 5.95-5.90 (1H, m), 5.80 (1H, br s), 4.45-4.20 (6H, m), 3.90-3.80 (4H, m), 3.65-3.50 (2H, m), 3.30 (3H, s).

Analysis : Found C, 63.91, H, 5.71, N, 13.35;  $C_{33}H_{35}N_8O_4Cl \cdot 0.33H_2O$  requires C, 63.82, H, 5.79, N, 13.54%.

EXAMPLE 30: (2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-Diphenylethyl)amino]-2-[(2-methoxybenzyl)amino]methyl}-9*H*-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol

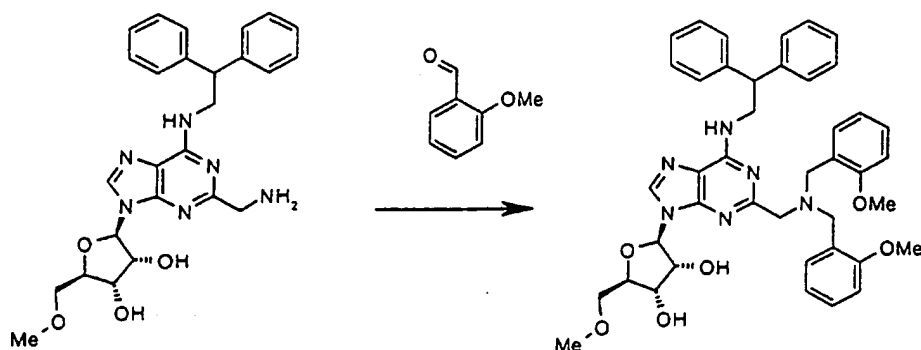


The title compound was prepared by a similar method to example 5 using (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (200mg, 0.4mmol), sodium triacetoxyborohydride (152mg, 0.72mmol) and 2-methoxybenzaldehyde (75mg, 0.53mmol). The product was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (95 : 5 : 0.5), which gave the title compound (53 mg) as a foam. MS: 611 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.85 (1H, br s), 7.30-7.10 (12H, m), 6.90-6.75 (2H, m), 6.10-5.90 (2H, m), 4.45-4.10 (6H, m), 3.90 (3H, s), 3.75-3.45 (4H, m), 3.30 (3H, s).

EXAMPLE 31: (2*R*,3*R*,4*S*,5*R*)-2-{2-[[Bis(2-methoxybenzyl)amino]methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol.



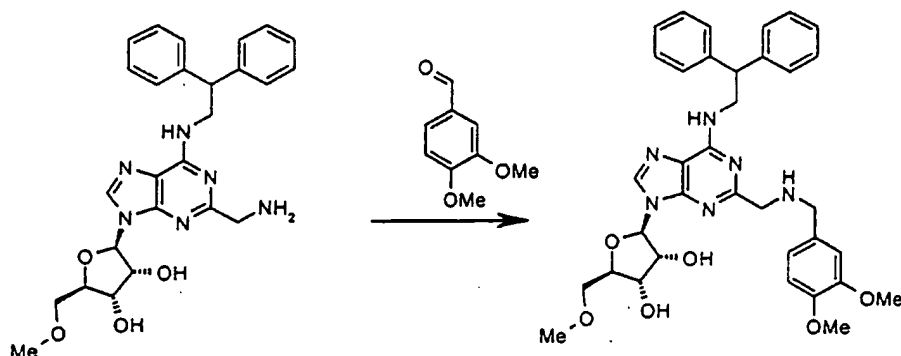


The title compound was prepared by a similar method to example 5 using (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (200mg, 0.4mmol), sodium triacetoxymethylborohydride (230mg, 0.72mmol) and 2-methoxybenzaldehyde (111mg, 0.82mmol). The product was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane : methanol (98 : 2) increasing in polarity to dichloromethane : methanol (93 : 7). This gave the title compound (130 mg) as a foam. MS: 731 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, br s), 7.75-7.65 (2H, m), 7.30-7.15 (14H, m), 6.90-6.75 (4H, m), 5.90 (1H, br s), 5.70 (1H, br s), 4.45-4.25 (6H, m), 3.95-3.80 (6H, m), 3.70 (6H, s), 3.65-3.50 (3H, m), 3.30 (3H, s).

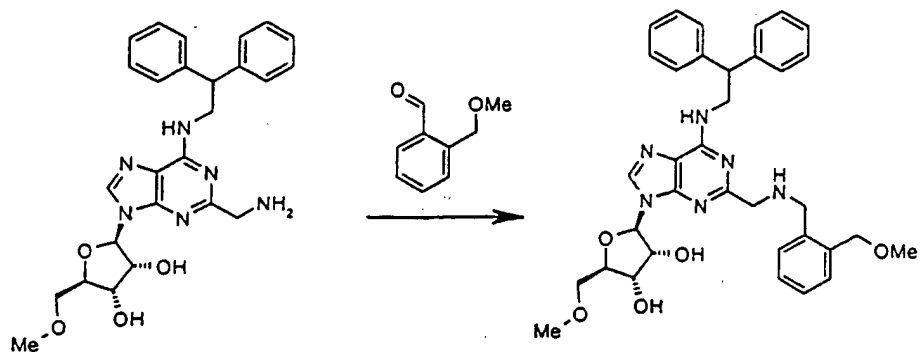
Analysis : Found C, 67.48, H, 6.34, N, 11.26; C<sub>42</sub>H<sub>46</sub>N<sub>6</sub>O<sub>6</sub>·H<sub>2</sub>O requires C, 67.38, H, 6.42, N, 11.23%.

**EXAMPLE 32:** (2*R*,3*R*,4*S*,5*R*)-2-(6-[(2,2-Diphenylethyl)amino]-2-[(4-isopropoxybenzyl)amino]methyl)-9*H*-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol.



- (2R,3R,4S,5R)-2-{2-(Aminomethyl)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (200mg, 0.4mmol) was dissolved in stirred tetrahydrofuran (5ml) and 3,4-dimethoxybenzaldehyde (130mg, 0.8mmol) added. The reagents were stirred together until everything had dissolved and then sodium triacetoxyborohydride (130mg, 0.6mmol) added. The reaction mixture was stirred for 24hr and then quenched by the addition of methanol (1 ml). The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane : methanol : ammonia (95 : 5 : 0.5) increasing to (92 : 7 : 1). This gave the title compound (90mg) as a foam. MS: 641 (MH<sup>+</sup>).
- <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.35-7.20 (10H, m), 6.95-6.70 (3H, m), 6.00-5.90 (1H, m), 5.85 (1H, br s), 4.40-4.20 (6H, m), 3.95-3.75 (10H, m), 3.65-3.50 (2H, m), 3.30 (3H, s).

- EXAMPLE 34:** (2R,3R,4S,5R)-2-[6-[(2,2-Diphenylethyl)amino]-2-[[2-(methoxymethyl)benzyl]amino]methyl]-9H-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol.



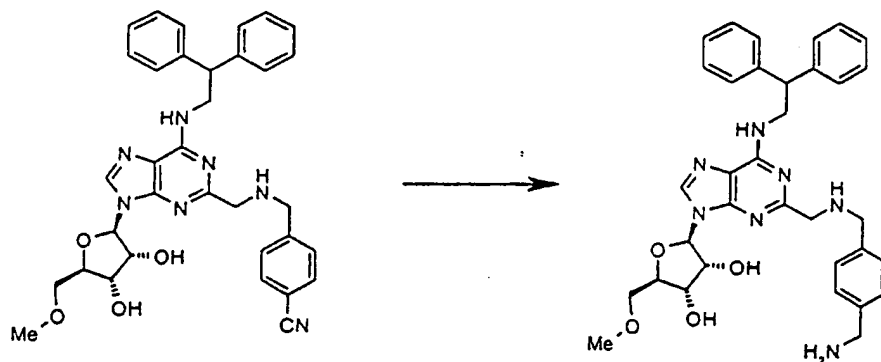
A solution of (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (323mg, 0.66mmol), 2-(methoxymethyl)benzaldehyde (109mg, 0.73mmol) (Tetrahedron 4739, 47, 1991) and 1 drop of acetic acid in tetrahydrofuran (15ml) was stirred at room temperature for 24hr. Sodium triacetoxyborohydride (310mg, 1.45mmol) was then added and the reaction mixture stirred for 1hr. At this point the solvent was partially removed under reduced pressure and the residue partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate solution. The solvent was removed from the organic layer under reduced pressure and the residue purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol (97 : 3) increasing in polarity to dichloromethane : methanol : ammonia (95 : 5 : 0.5). This gave the title compound (250mg) as a foam. MS: 625 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.95 (1H, s), 7.45-7.15 (14H, m), 6.00-5.90 (1H, m), 5.80 (1H, br s), 4.55 (2H, s), 4.45-4.25 (6H, m), 3.95 (4H, s), 3.70-3.50 (2H, m), 3.30 (6H, s).

Analysis : Found C, 64.11, H, 6.24, N, 12.78; C<sub>35</sub>H<sub>40</sub>N<sub>6</sub>O<sub>5</sub>·1.5H<sub>2</sub>O requires C, 64.51, H, 6.60, N, 12.90%.

#### EXAMPLE 35: (2*R*,3*R*,4*S*,5*R*)-2-{2-[[4-

(Aminomethyl)benzyl]amino}methyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol.

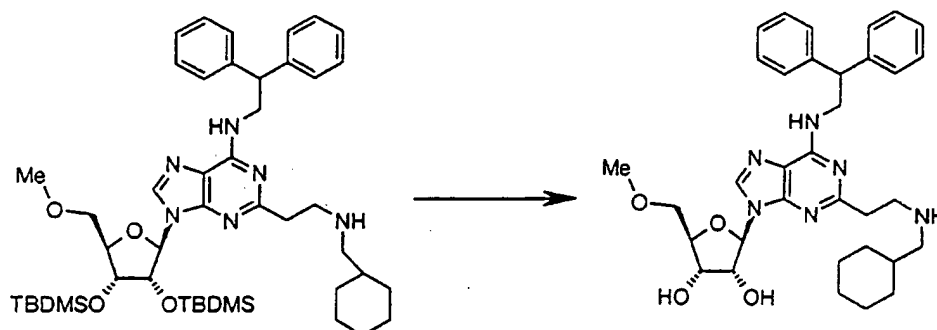


4-[[[(9-[(2R,3R,4S,5R)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-  
 [(2,2-diphenylethyl)amino]-9H-purin-2-yl)methyl]amino]methyl]benzonitrile  
 (example 42) (380mg, 0.62 mmol) was dissolved in a stirred saturated ethanolic  
 solution of ammonia (50ml) and Raney Nickel (200mg) added. The reaction  
 mixture was stirred under an atmosphere of 414kPa (60psi) of hydrogen for  
 24hr. The Raney Nickel was then filtered off through Arbocel (trade mark) and  
 the solvent removed from the filtrate under reduced pressure to give a residue  
 which was purified by column chromatography on silica gel eluting with a  
 solvent gradient of dichloromethane : methanol (97 : 3) increasing in polarity to  
 dichloromethane : methanol : ammonia (80 : 20 : 3). This gave the title  
 compound (260mg) as a gum. MS: 611 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub> + drop d<sub>6</sub> DMSO) δ = 7.85 (1H, s), 7.30-7.20 (10H, m), 7.20-  
 7.10 (4H, m), 5.90 (1H, d), 5.75 (1H, br s), 4.45-4.40 (1H, m), 4.35-4.15 (6H,  
 m), 3.85-3.75 (6H, m), 3.60-3.50 (2H, m), 3.30 (3H, s).

Analysis : Found C, 65.24, H, 6.26, N, 15.62; C<sub>34</sub>H<sub>39</sub>N<sub>7</sub>O<sub>4</sub>·H<sub>2</sub>O requires C,  
 65.07, H, 6.53, N, 15.62%.

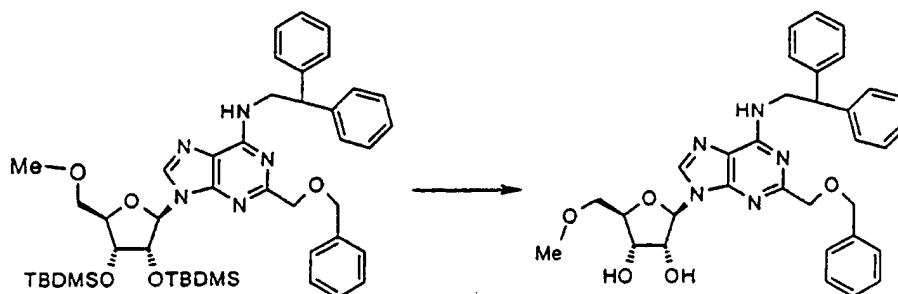
**Example 36: (2R,3R,4S,5R)-2-[2-{2-[(Cyclohexylmethyl)amino]ethyl}-6-  
 [(2,2-diphenylethyl)amino]-9H-purin-9-yl]-5-(methoxymethyl)tetrahydro-  
 3,4-furandiol**



*N*-(9-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis[[(*tert*-butyl(dimethyl)silyl]oxy)-5-(methoxymethyl)tetrahydro-2-furanyl]-2-{2-[(cyclohexylmethyl)amino]ethyl}-9*H*-purin-6-yl)-*N*-(2,2-diphenylethyl)amine (210 mg, 0.25mmol) (preparation 23) was dissolved in stirred tetrahydrofuran (1ml) and a 1M solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1ml, 1mmol) added. The reaction mixture was stirred at room temperature for 24hr. The solvent was removed under reduced pressure and the residue partitioned between dilute aqueous sodium hydroxide solution and ethyl acetate. The organic layer was separated and the aqueous phase extracted with ethyl acetate. The ethyl acetate phases were combined and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane : methanol : ammonia (94 : 6 : 0.6) increasing in polarity to (91 : 9 : 0.9). This gave the title compound (70 mg) as a powder. MS: 601 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.00 (1H, s), 7.35-7.20 (10H, m), 6.00-5.95 (1H, m), 5.75-5.70 (1H, m), 4.50-4.45 (1H, m), 4.40-4.20 (5H, m), 3.70-3.55 (2H, m), 3.30 (3H, s), 3.20-3.05 (3H, m), 2.75-2.65 (2H, m), 1.85-1.75 (2H, m), 1.75-1.60 (4H, m), 1.30-1.10 (4H, m), 1.00-0.80 (3H, m).

Analysis : Found C, 64.94, H, 7.33, N, 13.18;  $C_{34}H_{44}N_6O_4 \cdot 1.5H_2O$  requires C, 65.05, H, 7.55, N, 13.39%.



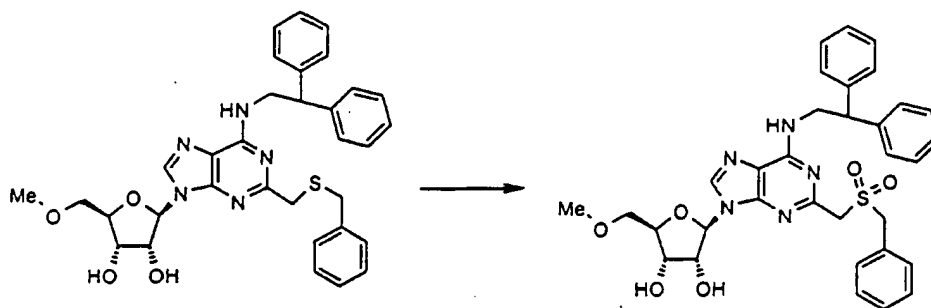
2-[(Benzyloxy)methyl]-9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis[[*tert*-butyl(dimethyl)silyl]oxy]-5-(methoxymethyl)tetrahydro-2-furanyl]-*N*-(2,2-diphenylethyl)-9*H*-purin-6-amine (65mg, 0.08mmol) (preparation 24) was dissolved in stirred tetrahydrofuran (10ml) and a 1 molar solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (0.5ml, 0.5mmol) added. The reaction mixture was stirred at room temperature for 15min. The solvent was removed under reduced pressure and the residue partitioned between saturated aqueous sodium hydrogen carbonate solution and ethyl acetate. The ethyl acetate layer was separated, washed with brine and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure to give a residue which was purified by column chromatography on silica gel eluting with a solvent system of ethyl acetate : hexane (3 : 1) increasing in polarity to ethyl acetate : methanol (97 : 3). This gave the title compound (25mg) as a gum. MS: 604 (MNa<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.00 (1H, s), 7.45-7.15 (15H, m), 6.50 (1H, br s), 6.05-6.00 (1H, m), 6.00-5.85 (1H, m), 4.70-4.55 (4H, m), 4.45-4.25 (6H, m), 3.65-3.50 (2H, m), 3.30 (3H, s).

20

**Example 39: (2*R*,3*R*,4*S*,5*R*)-2-{2-[(Benzylsulfonyl)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol**

25

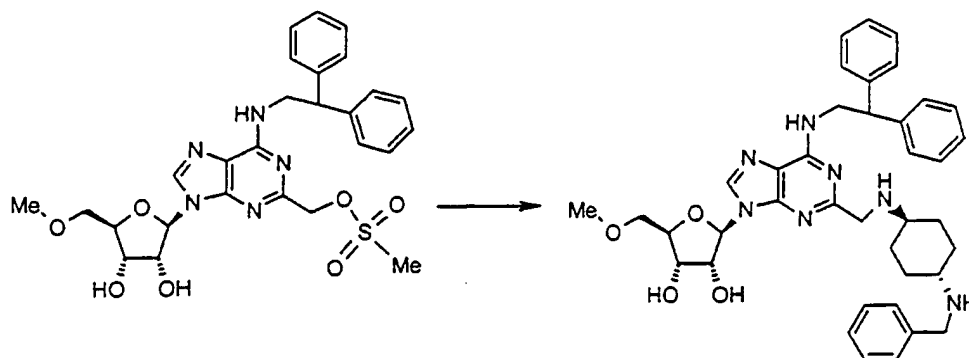


(2*R*,3*R*,4*S*,5*R*)-2-{2-[(Benzylsulfanyl)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-  
 purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (100mg, 0.17mmol)  
 (example 76) was dissolved in stirred acetone (3ml) and solid sodium hydrogen  
 5 carbonate (100mg, 1.2mmol) added. A solution of Oxone (trade mark)  
 (potassium peroxymonosulphate) (410mg, 0.68mmol) dissolved in water (2ml)  
 was then added dropwise to the original solution over the course of 30min.  
 Dichloromethane (2ml) was also added and the reaction mixture stirred at room  
 temperature for 60hr. The reaction mixture was then diluted with ethyl acetate  
 10 (100ml) and water (50ml). The organic layer was separated, dried with  
 anhydrous magnesium sulfate and the solvent removed under reduced  
 pressure to give a residue which was purified by column chromatography on  
 silica gel eluting with a solvent gradient of ethyl acetate : hexane (4 : 1)  
 increasing in polarity to ethyl acetate : methanol (96 : 4). This gave the title  
 15 compound (50 mg) as a gum. MS: 630 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.05 (1H, s), 7.55-7.45 (2H, m), 7.35-7.15 (13H, m), 6.05-  
 5.95 (2H, m), 5.25 (1H, s), 4.55-4.25 (10H, m), 3.70-3.55 (2H, m), 3.45 (1H, s),  
 3.35 (3H, s).

20

Example 40: (2*R*,3*R*,4*S*,5*R*)-2-{2-([trans-4-(Benzylamino)cyclohexyl]amino)methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-  
 purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol



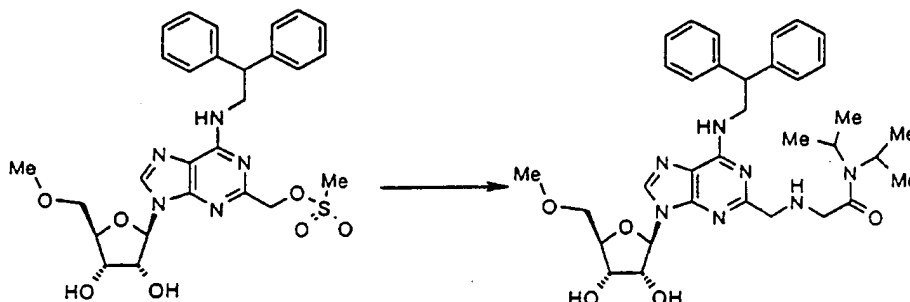
{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-  
 [(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl methanesulfonate (230mg,  
 0.4mmol) (preparation 25), *N*-(trans-4-aminocyclohexyl)benzylamine  
 5 (preparation 27) (160mg, 0.8mmol) and *N*-ethyl-*N*-isopropyl-2-propanamine  
 (100mg, 0.8mmol) were dissolved in a stirred mixture of ethanol (3ml) and  
 dichloromethane (12ml) and the reaction mixture stirred for 48hr at room  
 temperature. The solvent was then removed under reduced pressure and the  
 residue partitioned between ethyl acetate and water. The ethyl acetate layer  
 10 was separated, washed with brine and then dried with anhydrous magnesium  
 sulfate. The solvent was removed under reduced pressure and the residue  
 purified by column chromatography on silica gel eluting with a solvent gradient  
 of dichloromethane : methanol : ammonia (98 : 2 : 0.3) increasing in polarity to  
 (90 : 10 : 1). The residue after solvent evaporation was triturated with diethyl  
 15 ether to give the title compound (26 mg) as a solid. MS: 678 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.35-7.15 (15H, m), 5.90-5.80 (2H, m), 4.40-  
 4.20 (6H, m), 3.90 (2H, s), 3.80 (2H, s), 3.65-3.55 (2H, m), 3.30 (3H, s), 2.60-  
 2.45 (2H, m), 2.05-1.90 (4H, m) 1.25-1.05 (4H, m).

20

**Example 41: 2-[(9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-  
 (methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-  
 purin-2-yl)methylamino]-*N,N*-diisopropylacetamide**





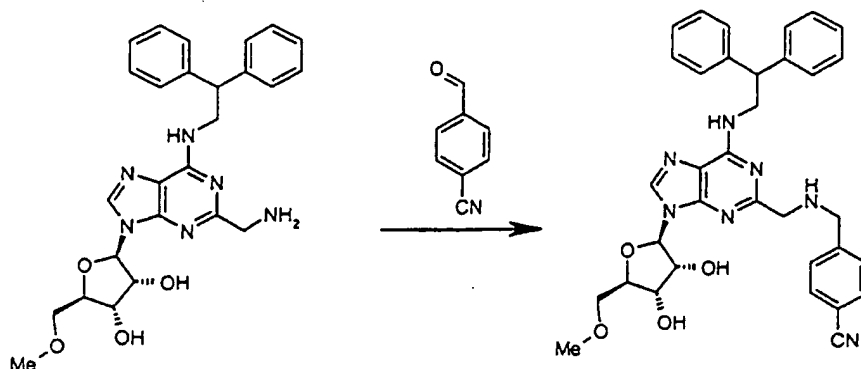
The title compound was prepared by a similar method to example 40 using {9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl methanesulfonate (preparation 25)  
 5 (374mg, 0.66mmol), 2-amino-*N,N*-diisopropylacetamide (520mg, 3.3mmol) (preparation 22) and *N*-ethyl-*N*-isopropyl-2-propanamine (170mg, 1.32mmol). The compound was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane : methanol : ammonia (95 : 5 : 0.5) increasing in polarity to (90 : 10 : 1). The solvent was removed under reduced  
 10 pressure to give a residue which was triturated with diethyl ether to give the title compound (47 mg) as a solid. MS: 632 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.35-7.15 (10H, m), 5.95-5.90 (1H, m), 5.70 (1H, s), 4.70-4.65 (1H, m), 4.60-4.55 (1H, m), 4.40-4.25 (4H, m), 4.05-3.85 (3H, m), 3.70-3.65 (1H, m), 3.60-3.45 (5H, m), 3.35 (3H, s), 1.35 (6H, d), 1.20 (6H, d).  
 15

Analysis : Found C, 62.51, H, 7.03, N, 14.85; C<sub>34</sub>H<sub>45</sub>N<sub>7</sub>O<sub>5</sub>·1.1H<sub>2</sub>O requires C, 62.62, H, 7.24, N, 15.04%.

20

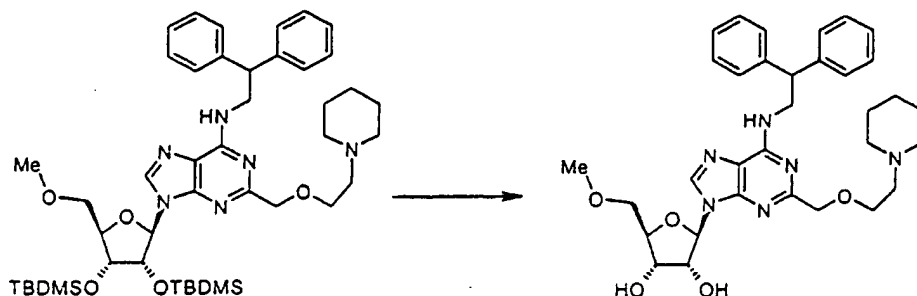
**EXAMPLE 42:** 4-[[[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl]amino]methyl]benzonitrile.



The title compound was prepared by a similar method to example 5 from (2R,3R,4S,5R)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (400mg, 0.82mmol), sodium triacetoxyborohydride (260mg, 1.22mmol) and 4-cyanobenzaldehyde (120mg, 0.9mmol). The product was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol : ammonia (92 : 7 : 1) gradually increasing polarity to dichloromethane : methanol : ammonia (90 : 10 : 1), which gave the title compound (210 mg) as a foam. MS: 606 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.95 (1H, s), 7.60-7.55 (2H, m), 7.55-7.45 (2H, m), 7.40-7.20 (10H, m), 5.95-5.90 (1H, m), 5.85 (1H, br s), 4.50-4.20 (6H, m), 3.95-3.85 (4H, m), 3.65-3.55 (2H, m), 3.35 (3H, s).

**EXAMPLE 43:** (2R,3R,4S,5R)-2-(6-[(2,2-Diphenylethyl)amino]-2-[[2-(1-piperidinyl)ethoxy]methyl]-9H-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol.



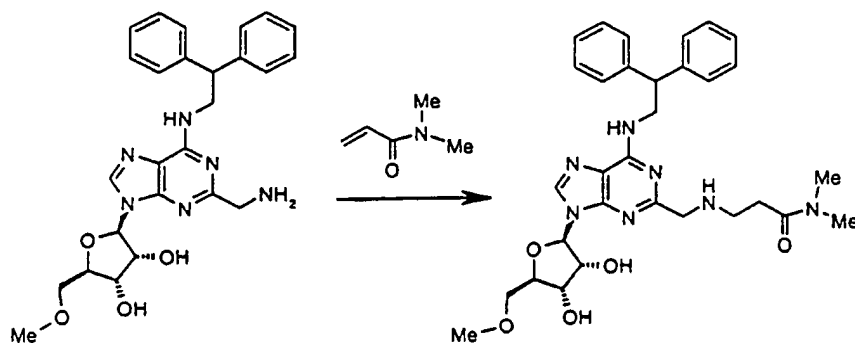
The title compound was prepared by a similar method to example 38 using *N*-(9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis[*tert*-(dimethyl)silyloxy]-5-(methoxymethyl)tetrahydro-2-furanyl]-2-[[2-(1-piperidinyl)ethoxy]methyl]-9*H*-purin-6-yl)-*N*-(2,2-diphenylethyl)amine (100mg, 0.12mmol) (preparation 29),  
 5 and a 1M solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (0.5ml, 0.5mmol). The compound was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (95 : 5 : 0.5) to give the title compound (22mg) as a gum. MS: 604 (MH<sup>+</sup>).

10

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.15 (1H, s), 7.35-7.20 (10H, m), 6.15 (1H, s), 5.70 (1H, br s), 4.70-4.55 (2H, m), 4.45-4.15 (6H, m), 3.90-3.75 (3H, m), 3.70-3.60 (1H, m), 3.45 (3H, s), 2.80-2.40 (6H, m), 1.75-1.65 (4H, m), 1.55-1.45 (2H, m).

15

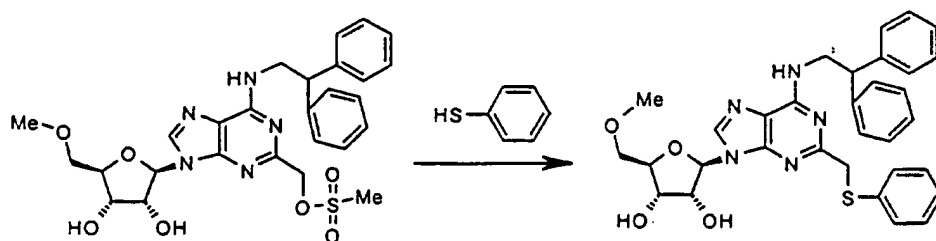
**EXAMPLE 44:** 3-[(9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl]amino]-*N,N*-dimethylpropanamide.



(2*R*,3*R*,4*S*,5*R*)-2-{2-(Aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (200mg, 0.39mmol) was dissolved in stirred methanol (10ml) and *N,N*-dimethylacrylamide (40mg, 0.39mmol) added. The reaction mixture was stirred for 120hr at room temperature and then 50°C for a further 24hr. More *N,N*-dimethylacrylamide (9mg, 0.1mmol) was added and the reaction mixture was heated at 50°C for 30hr. A further portion of *N,N*-dimethylacrylamide (10mg, 0.1mmol) was added and the reaction mixture heated to 50°C for a further 24hr. The solvent was then removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (94 : 4 : 0.2) increasing in polarity to (93 : 7 : 0.3) to give the title compound (100mg) as a foam. MS: 590 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.95 (1H, s), 7.35-7.20 (10H, m), 6.00 (1H, s), 5.60 (1H, br s), 4.65-4.60 (2H, m), 4.40-4.15 (4H, m), 4.05-3.90 (2H, m), 3.80-3.75 (1H, m), 3.65-3.60 (1H, m), 3.40 (3H, s), 3.05 (3H, s), 3.00-2.95 (5H, m), 2.75-2.55 (2H, m).

**EXAMPLE 45: (2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-Diphenylethyl)amino]-2-[(phenylsulfanyl)methyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol.**

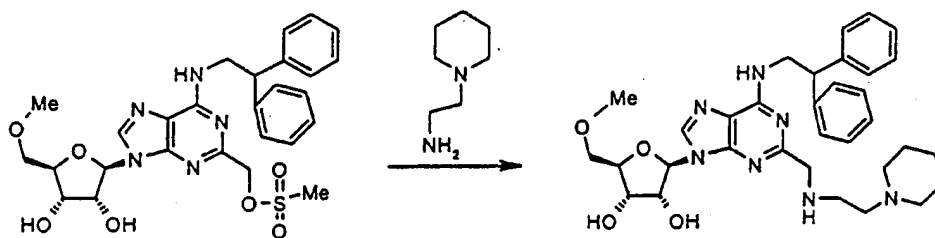


{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl methanesulfonate (400mg, 0.7mmol) (Preparation 25), triethylamine (0.2ml, 1.4mmol) and thiophenol (100mg, 0.9mmol) were dissolved in tetrahydrofuran (3ml) and the reaction

mixture stirred for 24hr at room temperature. The solvent was then removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane : methanol (99 : 1) increasing in polarity to (95 : 5). This gave the title compound (150mg) as a  
 5 foam. MS: 584 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 7.90 (1H, s), 7.50-7.40 (2H, m), 7.40-7.10 (13H, m), 5.85-5.70 (2H, m), 4.45-4.20 (9H, m), 3.60-3.50 (2H, m), 3.30 (3H, s), 3.05 (1H, s).

10 **EXAMPLE 46: (2R,3R,4S,5R)-2-[6-[(2,2-Diphenylethyl)amino]-2-{{[2-(1-piperidiny)ethyl]amino}methyl}-9H-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol.**

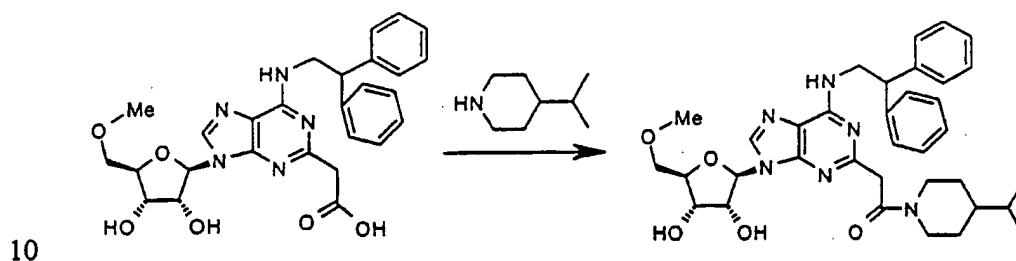


15 {9-[(2R,3R,4S,5R)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9H-purin-2-yl)methyl methanesulfonate (150mg, 0.26mmol) (Preparation 25) was dissolved in stirred dichloromethane (5ml) and 2-(1-piperidiny)ethylamine (0.2ml, 1.3mmol) added. The reaction mixture was stirred for 24hr at room temperature. The solvent was removed from the  
 20 reaction mixture under reduced pressure and the residue partitioned between dichloromethane (100ml) and water (50ml). The organic layer was separated and washed with water (50ml), followed by removal of solvent under reduced pressure and purification of the residue by column chromatography on silica gel eluting with a solvent gradient of dichloromethane : methanol (95 : 5) increasing  
 25 in polarity to dichloromethane : methanol : ammonia (90 : 10 : 1). This gave title compound (40mg) as a gum. MS: 603 (MH<sup>+</sup>).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 8.05 (0.15H, br s), 7.95 (0.85H, s), 7.35-7.15 (10H, m), 6.05-6.00 (1H, m), 5.70 (1H, br s), 4.50-3.85 (10H, m), 3.75-3.70 (1H, m), 3.60-3.55 (1H, m), 3.35 (3H, s), 2.95-2.75 (2H, m), 2.65-2.55 (0.3H, m), 2.55-2.45 (1.7H, m), 2.45-2.30 (4H, m), 1.60-1.55 (4H, m), 1.45-1.35 (2H, m).

5

**EXAMPLE 47: 2-{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}-1-(4-isopropyl-1-piperidinyl)-1-ethanone.**



4-Isopropylpiperidine (J. Am. Chem. Soc. 2592, 68, 1946) (105mg, 0.64mmol) was added to a stirred solution of 2-{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}acetic acid (300mg, 0.58mmol) (preparation 51), *N,N'*-dicyclohexylcarbodiimide (150mg, 0.64mmol), 1*H*-1,2,3-benzotriazol-1-ol monohydrate (110mg, 0.71mmol) and *N*-ethyl-*N*-isopropyl-2-propanamine (190mg, 1.47mmol) in dichloromethane (15ml). The reaction mixture was stirred for 24hr at room temperature. The solvent was then removed under reduced pressure, then the residue treated with ethyl acetate and the mixture filtered.

20 The solid was washed with ethyl acetate and the combined ethyl acetate filtrates washed with saturated aqueous sodium hydrogen carbonate solution, brine and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (95 : 5 : 0.5) to give some pure and some impure material. The

25 impure material was then re-purified by column chromatography on silica gel eluting with a solvent gradient of ethyl acetate increasing in polarity to ethyl

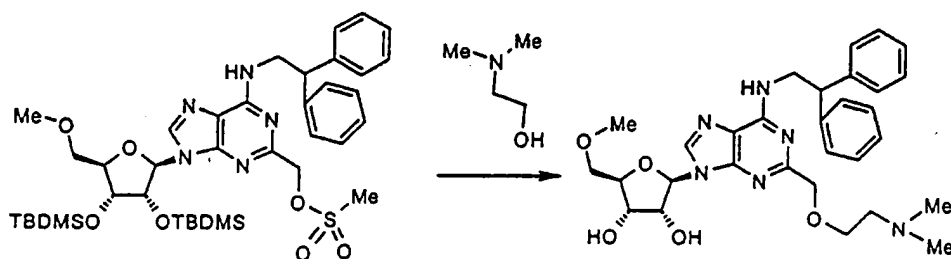
acetate : methanol (95 : 5). The pure fractions from both columns were combined to give the title compound (285mg) as a foam. MS: 629 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, br s), 7.35-7.20 (10H, m), 6.20-6.05 (1H, m),  
 5.95-5.90 (1H, m), 5.70 (1H, br s), 4.70-4.60 (1H, m), 4.45-4.40 (1H, m), 4.40-  
 4.20 (5H, m), 4.05-3.85 (3H, m), 3.60-3.50 (3H, m), 3.35-3.30 (3H, m), 2.95-  
 2.85 (1H, m), 2.55-2.45 (1H, m), 1.70-1.60 (1H, m), 1.60-1.55 (1H, m), 1.40-  
 1.30 (1H, m), 1.20-1.10 (2H, m), 1.05-0.95 (1H, m), 0.85-0.75 (6H, m).

10

**EXAMPLE 48: (2*R*,3*R*,4*S*,5*R*)-2-{2-[2-(Dimethylamino)ethoxy]methyl}-6-  
 [(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-  
 3,4-furandiol**

15



20

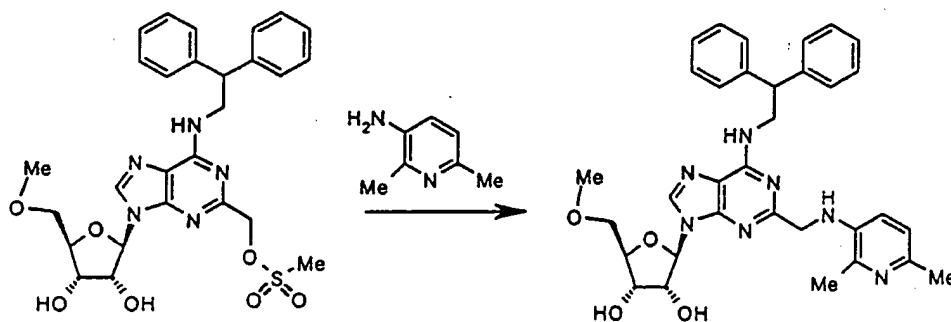
Potassium *tert* butoxide (112mg, 1mmol) was added to a stirred solution of {9-  
 [(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-  
 (methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-  
 yl)methyl methanesulfonate (200mg, 0.25mmol) (preparation 16) and 2-(*N,N*-  
 dimethylamino)ethanol (0.16ml, 1.5mmol) in *N,N*-dimethylformamide (3ml). The  
 reaction was quenched by the addition of saturated aqueous ammonium  
 chloride solution (30ml) after 30min. The aqueous phase was extracted with  
 dichloromethane (60ml). The organic phase was separated, dried with  
 anhydrous magnesium sulfate and the solvent removed under reduced  
 pressure to give a residue that was azeotroped with toluene to remove traces of  
*N,N*-dimethylformamide. This was then purified by column chromatography on

25

silica gel eluting with a solvent gradient of dichloromethane : methanol : ammonia (94 : 5 : 1) increasing in polarity to (84 : 14 : 2) to give the title compound (33mg) as a foam. MS: 563 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 8.15 (1H, s), 7.35-7.20 (10H, m), 6.10 (1H, s), 5.85 (1H, br s), 4.70-4.55 (2H, m), 4.45-4.20 (8H, m), 3.85-3.80 (1H, m), 3.80-3.75 (2H, m), 3.65-3.60 (1H, m), 3.45 (3H, s), 2.75-2.60 (2H, m), 2.40 (6H, s).

**EXAMPLE 49: (2*R*,3*R*,4*S*,5*R*)-2-{2-[(2,6-Dimethyl-3-pyridinyl)amino]methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol**



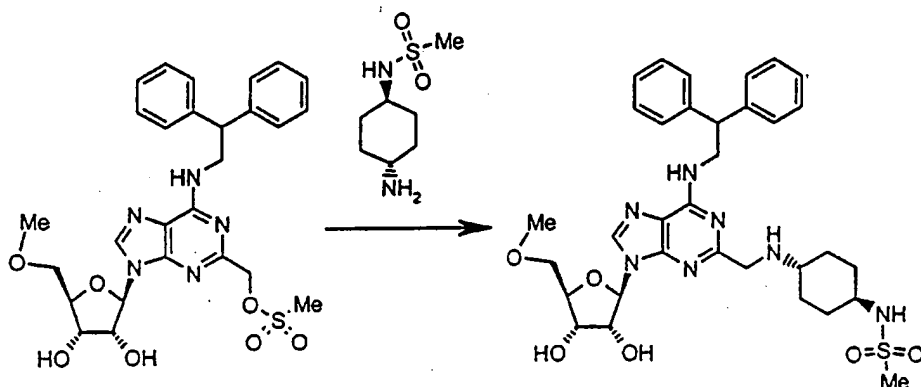
{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl methanesulfonate (preparation 25) (75mg, 0.13mmol) was added to a solution of 2,6-dimethyl-3-pyridinylamine (22mg, 0.17mmol) and triethylamine (0.036ml, 0.26mmol) in ethyl acetate (3ml) and *N,N*-dimethylformamide (1ml) in the reaction vessel of a Argonaut Quest 210 machine. The reaction mixture was agitated and heated to 60°C for 12hr. More 2,6-dimethyl-3-pyridinylamine (22mg, 0.17mmol) and triethylamine (0.036ml, 0.26mmol) were added and heating and agitation continued for a further 24hr. The reaction mixture was then washed with water and the organic phase separated and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a residue which was purified by reverse phase HPLC using firstly a Lana C<sub>8</sub> (2) column and then a Magellan C<sub>18</sub> column eluting with 5mM ammonium acetate in water : 2mM ammonium



acetate in acetonitrile (90 : 10) decreasing in polarity to 5mM ammonium acetate in water : 2mM ammonium acetate in acetonitrile (10 : 90) as eluant. This gave the title compound (9mg) as a gum. MS: 596 (MH<sup>+</sup>).

- 5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.95 (1H, s), 7.35-7.20 (10H, m), 6.85-6.70 (2H, m), 6.10-6.00 (1H, m), 5.95-5.90 (1H, m), 4.45-4.40 (1H, m), 4.40-4.25 (7H, m), 3.70-3.50 (2H, m), 3.35 (3H, s), 2.40-2.30 (6H, m).

- 10 **EXAMPLE 50:** *N*-{4-[[{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl]amino}trans-cyclohexyl}methanesulfonamide.

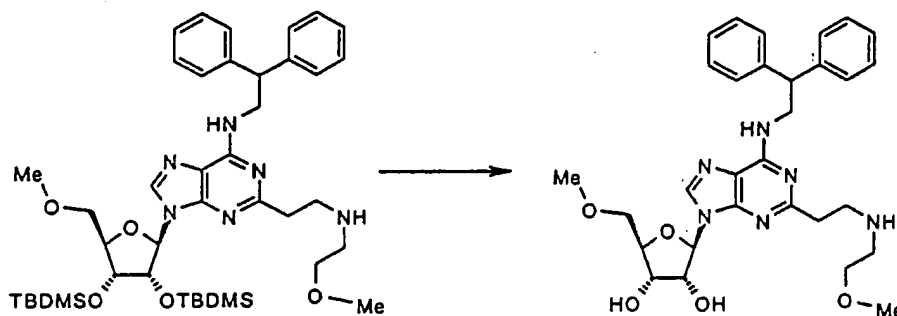


- N*-(trans-4-Aminocyclohexyl)methanesulfonamide (183mg, 0.8mmol)  
 15 (preparation 33) was added to a stirred solution of {9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl methanesulfonate (230mg, 0.4mmol) (preparation 25) and *N*-ethyl-*N*-isopropyl-2-propanamine (210mg, 1.6mmol) in ethanol (3ml) and dichloromethane (12ml). The reaction mixture was stirred for 48hr at room  
 20 temperature. The solvent was then removed under reduced pressure and the residue partitioned between ethyl acetate and water. The ethyl acetate layer was separated, washed with brine and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a residue which was purified by column chromatography on silica gel eluting with a  
 25 solvent gradient of dichloromethane : methanol : ammonia (98 : 2 : 0.3)

increasing in polarity to (90 : 10 : 1) to give the title compound (50mg) as a foam. MS: 667 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) Mixture of Rotamers  $\delta$  = 8.00 (0.2H, s), 7.95 (0.8H, s), 7.35-7.20 (10H, m), 6.00-5.85 (2H, m), 4.40-4.20 (8H, m), 4.00-3.85 (2H, m), 3.70-3.55 (2H, m), 3.35 (0.6H, s), 3.30 (2.4H, s), 3.30-3.20 (1H, m), 2.95 (2.4H, s), 2.90 (0.6H, s), 2.65-2.50 (1H, m), 2.10-1.95 (4H, m), 1.35-1.15 (4H, m).

**EXAMPLE 51: (2*R*,3*R*,4*S*,5*R*)-2-(6-[(2,2-Diphenylethyl)amino]-2-{2-[(2-methoxyethyl)amino]ethyl}-9*H*-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol.**

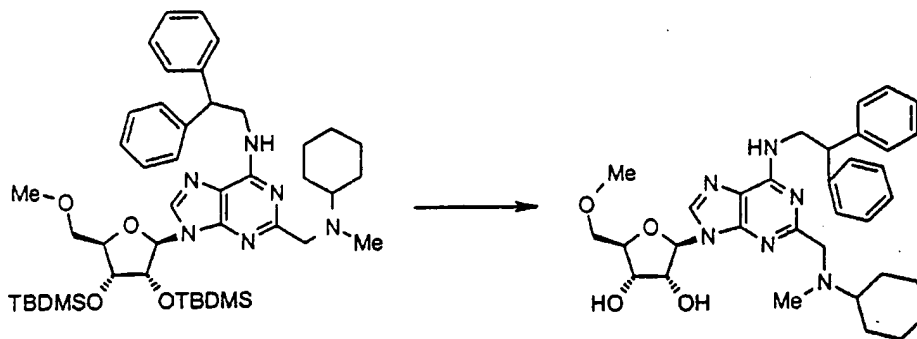


The title compound was prepared by a similar method to example 38 using *N*-(2-{9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis[*tert*-butyl(dimethyl)silyl]oxy]-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}ethyl)-*N*-(2-methoxyethyl)amine (150 mg, 0.19mmol) (preparation 34) and a 1 molar solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (0.5ml, 0.5mmol). The compound was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane : methanol : ammonia (94 : 6 : 0.6) increasing in polarity to (90 : 10 : 1) to give the title compound (50mg) as a foam. MS: 563 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 7.95 (1H, s), 7.35-7.20 (10H, m), 5.95-5.90 (1H, m), 5.65 (1H, br s), 4.50-4.45 (1H, m), 4.40-4.20 (5H, m), 3.70-3.65 (1H, m), 3.60-3.50 (3H, m), 3.35 (3H, s), 3.30 (3H, s), 3.15-3.00 (4H, m), 2.90-2.85 (2H, m).

Analysis : Found C, 61.20, H, 6.79, N, 14.07;  $C_{30}H_{38}N_6O_5 \cdot 1.5H_2O$  requires C, 61.10, H, 7.01, N, 14.25%.

- 5 **EXAMPLE 52: (2R,3R,4S,5R)-2-{2-[[Cyclohexyl(methyl)amino]methyl]-6-[[2,2-diphenylethyl]amino]-9H-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol**



- 10 *N*-(9-[(2R,3R,4R,5R)-3,4-Bis[*tert*-butyl(dimethyl)silyl]oxy]-5-(methoxymethyl)tetrahydro-2-furanyl)-2-[[cyclohexyl(methyl)amino]methyl]-9H-purin-6-yl)-*N*-(2,2-diphenylethyl)amine (133mg, 0.16mmol) (preparation 35) was dissolved in stirred tetrahydrofuran (1ml) and a 1 molar solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1ml, 1mmol) was added. The reaction mixture was stirred for 1hr, then the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (95 : 5 : 0.5) to give the title compound (83mg) as a foam. MS: 587 (MH<sup>+</sup>).

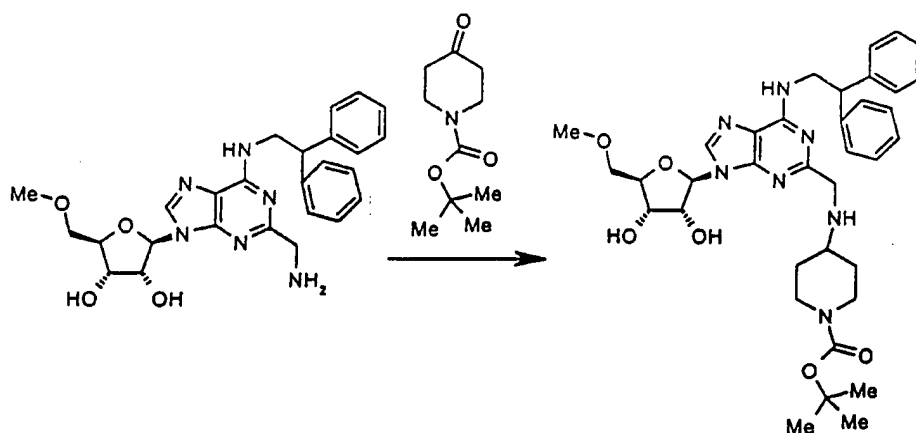
20

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.35-7.20 (10H, m), 5.90-5.85 (1H, m), 5.65 (1H, br s), 4.45-4.25 (6H, m), 3.75 (2H, br s), 3.60-3.50 (2H, m), 3.30 (4H, s), 2.55-2.30 (4H, m), 1.95-1.85 (2H, m), 1.80-1.75 (2H, m), 1.65-1.60 (1H, m), 1.35-1.20 (5H, m).

25

Analysis : Found C, 65.65, H, 7.09, N, 13.70;  $C_{33}H_{42}N_6O_4 \cdot H_2O$  requires C, 65.54, H, 7.33, N, 13.90%.

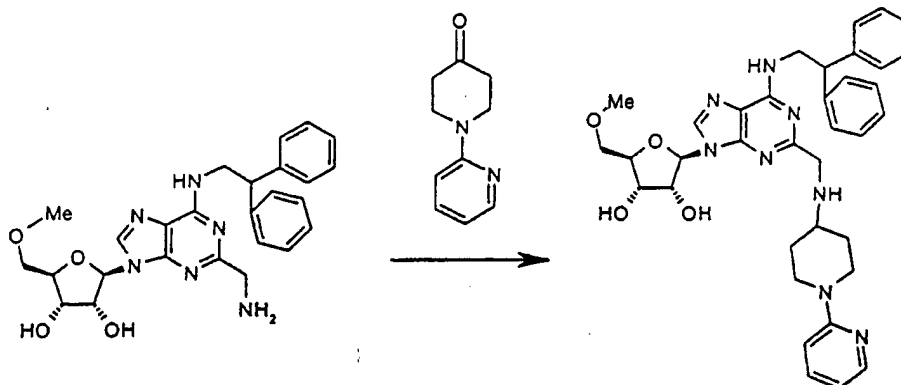
**EXAMPLE 53:** *tert*-Butyl 4-[(9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl]amino]-1-piperidinecarboxylate



The title compound was prepared by a similar method to example 6 using (2*R*,3*R*,4*S*,5*R*)-2-[2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (250mg, 0.51mmol), *tert*-butyl 4-oxo-1-piperidinecarboxylate (100mg, 0.51mmol), sodium triacetoxyborohydride (162mg, 0.75mmol) and acetic acid (30mg, 0.5mmol) in tetrahydrofuran (20ml). The product was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (92.3 : 6.7 : 0.33) to give the title compound (260mg) as a solid.  $R_f$  0.66 in dichloromethane : methanol : ammonia (80 : 20 : 1).

$^1H$  NMR ( $CDCl_3$ )  $\delta$  = 7.90 (1H, s), 7.35-7.20 (10H, m), 5.95-5.85 (2H, m), 4.45-4.25 (6H, m), 4.05-3.95 (2H, m), 3.90 (2H, s), 3.65-3.55 (2H, m), 3.35 (3H, s), 2.85-2.65 (3H, m), 1.90-1.60 (4H plus HOD in  $CDCl_3$ , m), 1.50 (9H, s), 1.40-1.25 (2H, m).

**EXAMPLE 54:** (2*R*,3*R*,4*S*,5*R*)-2-[6-[(2,2-Diphenylethyl)amino]-2-[[1-(2-pyridinyl)-4-piperidinyl]amino}methyl]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol.



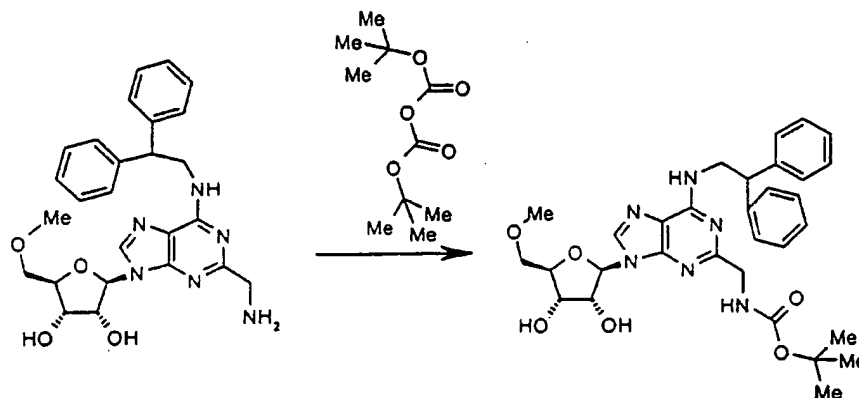
5

The title compound was prepared by a similar method to example 6 using (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (300mg, 0.6mmol),  
 10 acetic acid (45mg, 0.72mmol), sodium triacetoxyborohydride (200mg, 0.91mmol) and 1-(2-pyridinyl)-4-piperidinone (120mg, 0.66mmol) (preparation 37). The product was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (96 : 4 : 0.2) increasing in polarity to (93 : 7 : 0.3) to give the title compound (199mg) as a  
 15 foam. MS: 653 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.20-8.15 (1H, m), 7.90 (1H, s), 7.50-7.40 (1H, s), 7.35-7.15 (10H, m), 6.65-6.60 (1H, m), 6.60-6.55 (1H, m), 5.95-5.90 (1H, m), 5.80 (1H, br s), 4.40-4.15 (8H, m), 3.95 (2H, s), 3.65-3.50 (2H, m), 3.30 (3H, s),  
 20 2.95-2.75 (3H, m), 2.00-1.90 (2H, m), 1.55-1.40 (2H, m).

Analysis : Found C, 64.30, H, 6.38, N, 16.45; C<sub>36</sub>H<sub>42</sub>N<sub>8</sub>O<sub>4</sub>·0.5H<sub>2</sub>O·0.14CH<sub>2</sub>Cl<sub>2</sub> requires C, 64.60, H, 6.49, N, 16.68%.

**EXAMPLE 55:** *tert*-Butyl {9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methylcarbamate.



- 5 Di-*tert*-butyl dicarbonate (88mg, 0.4mmol) was added to a stirred solution of (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)-tetrahydro-3,4-furandiol (example 1) (210mg, 0.43mmol) in tetrahydrofuran (20ml). The reaction mixture was stirred at room temperature for 30min, the solvent was removed under reduced pressure and the residue
- 10 purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol (95 : 5) to give the title compound (210mg) as a foam. MS: 591 (MH<sup>+</sup>).

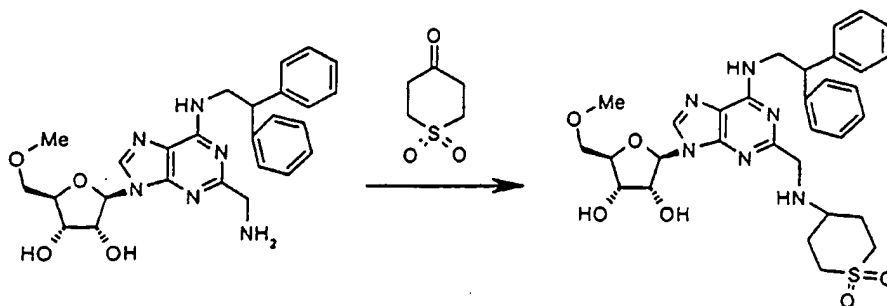
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.35-7.20 (10H, m), 5.95-5.80 (2H, m), 5.50 (1H, br s), 4.50-4.25 (8H, m), 3.65-3.55 (2H, m), 3.35 (3H, s), 3.20 (1H, br s), 1.45 (9H, s).

15

Analysis : Found C, 61.12, H, 6.30, N, 13.65; C<sub>31</sub>H<sub>37</sub>N<sub>6</sub>O<sub>6</sub>·0.5H<sub>2</sub>O·0.1CH<sub>2</sub>Cl<sub>2</sub> requires C, 61.52, H, 6.34, N, 13.84%.

20

**EXAMPLE 56:** 4-[(9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl]amino]tetrahydro-1*λ*<sup>6</sup>-thiopyran-1,1(2*H*)-dione.



The title compound was prepared by a similar method to example 6 using (2*R*,3*R*,4*S*,5*R*)-2-[2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol (305mg, 0.60mmol) (example 1),  
 5 tetrahydro-1λ<sup>6</sup>-thiopyran-1,1,4-trione (88mg, 0.60mmol), sodium triacetoxymethylborohydride (200mg, 0.90mmol) and acetic acid (43mg, 0.72mmol). The product was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (96 : 4 : 0.2) to give the title compound (160mg) as a foam. MS: 623 (MH<sup>+</sup>).

10

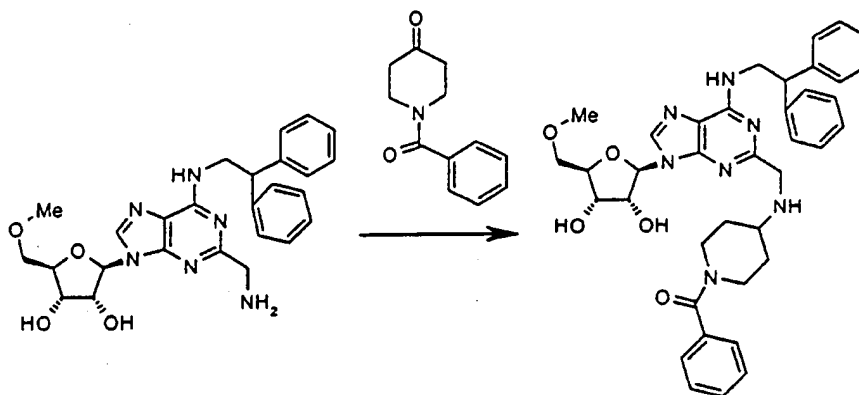
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.35-7.20 (10H, m), 6.10 (1H, br s), 5.95-5.90 (1H, m), 5.85 (1H, br s), 4.50-4.45 (1H, m), 4.40-4.20 (5H, m), 3.85 (2H, br s), 3.65-3.55 (2H, m), 3.40-3.30 (5H, m), 3.20 (1H, br s), 3.00-2.95 (1H, m), 2.85-2.75 (2H, m), 2.30-2.20 (2H, m), 2.15-2.00 (2H, m).

15

Analysis : Found C, 56.26, H, 5.79, N, 12.48; C<sub>31</sub>H<sub>38</sub>N<sub>8</sub>O<sub>6</sub>S. 0.5CH<sub>2</sub>Cl<sub>2</sub> requires C, 55.98, H, 5.91, N, 12.63%.

**EXAMPLE 57:** {4-[(9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl]amino]-1-piperidiny](phenyl)methanone

20



The title compound was prepared by a similar method to example 6 using (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (310mg, 0.63mmol) (example 1), 1-benzoyl-4-piperidinone (128mg, 0.63mmol), sodium triacetoxyborohydride (200mg, 0.90mmol) and acetic acid (45mg, 0.74mmol). The product was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (92 : 8 : 0.4) to give the title compound (300mg) as an oil. MS: 679 (MH<sup>+</sup>).

10

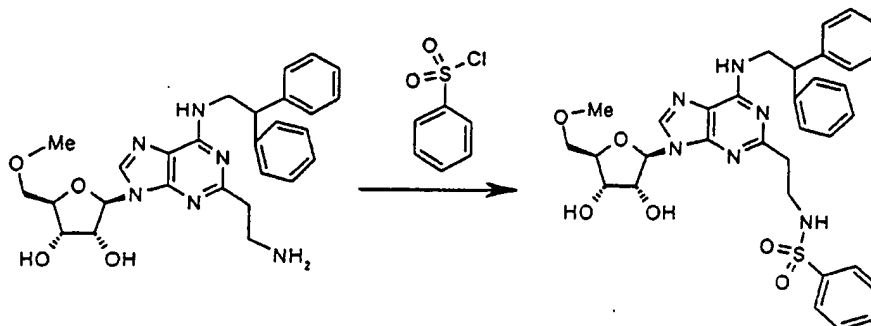
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.45-7.20 (15H, m), 5.95-5.90 (2H, m), 4.50 (1H, br s), 4.45-4.20 (6H, m), 3.90 (2H, s), 3.70 (1H, br s), 3.65-3.55 (2H, m), 3.35 (3H, s), 3.05-2.80 (3H, m), 2.10-1.80 (2H, m), 1.50-1.30 (2H, m).

15 Analysis : Found C, 64.35, H, 6.16, N, 13.63; C<sub>38</sub>H<sub>43</sub>N<sub>7</sub>O<sub>5</sub>·0.5H<sub>2</sub>O·0.33CH<sub>2</sub>Cl<sub>2</sub> requires C, 64.38, H, 6.29, N, 13.71%.

**EXAMPLE 58:** *N*-(2-{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}ethyl)benzenesulfonamide

20



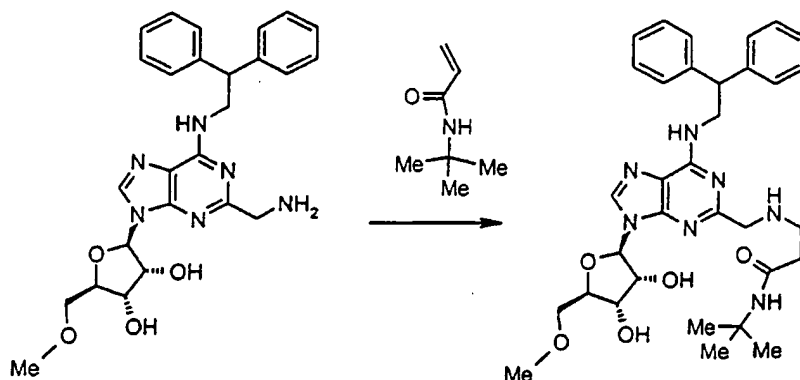


The title compound was prepared by a similar method to example 3 using (2*R*,3*R*,4*S*,5*R*)-2-{2-(2-aminoethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)-tetrahydro-3,4-furandiol (example 11) (200mg, 0.40mmol), phenylsulfonyl chloride (70mg, 0.40mmol) and triethylamine (0.15ml, 1.08mmol). The compound was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol (95 : 5) to give the title compound (145mg) as a powder. MS: 645 (MH<sup>+</sup>).

- 10 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.80-7.75 (2H, m), 7.50-7.45 (1H, m), 7.45-7.20 (12H, m), 6.45-6.35 (1H, m), 5.95-5.90 (1H, m), 5.75 (1H, br s), 5.30 (1H, s), 4.50-4.15 (6H, m), 3.70-3.55 (2H, m), 3.45-3.35 (6H, m), 3.15-3.10 (1H, m), 3.00-2.85 (2H, m).
- 15 Analysis : Found C, 60.77, H, 5.66, N, 12.96; C<sub>33</sub>H<sub>36</sub>N<sub>6</sub>O<sub>6</sub>S.0.25H<sub>2</sub>O requires C, 61.05, H, 5.67, N, 12.94%.

**EXAMPLE 59:** *N*-(*tert*-Butyl)-3-[(9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl]amino]propanamide.

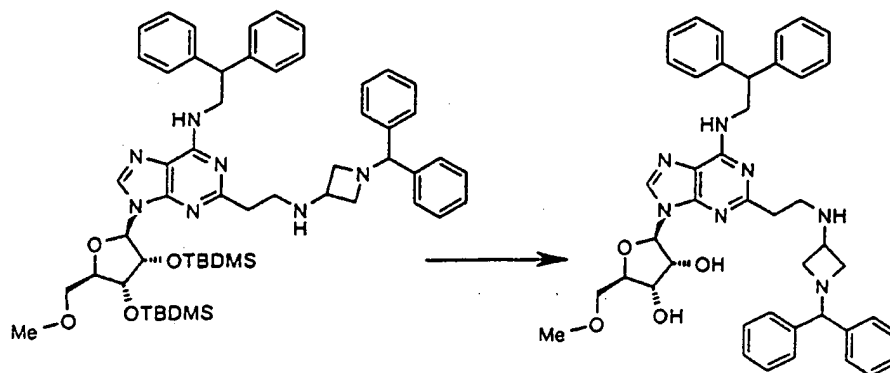
20



(2*R*,3*R*,4*S*,5*R*)-2-{2-(Aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (example 1) (250mg, 0.48mmol) was dissolved in stirred methanol (10ml) and *N*-(*tert*-butyl)acrylamide (62mg, 0.48mmol) added. The reaction mixture was stirred for 24hr at room temperature and then heated at reflux for 120hr, at which time all solvent had evaporated. The residual reaction mixture was dissolved in dichloromethane and the solvent removed under reduced pressure, this procedure was repeated twice more and then the product purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane : methanol : ammonia (94 : 4 : 0.2) increasing in polarity to (93 : 7 : 0.3) to give the title compound (143mg) as a foam. MS: 618 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.95 (1H, s), 7.35-7.20 (10H, m), 6.15 (1H, br s), 5.95 (1H, s), 5.65 (1H, br s), 4.60-4.50 (2H, m), 4.40-4.25 (4H, m), 4.00-3.85 (2H, m), 3.75-3.70 (1H, m), 3.65-3.60 (1H, m), 3.35 (3H, s), 3.00-2.90 (1H, m), 2.90-2.80 (1H, m), 2.40-2.35 (2H, m), 1.30 (9H, s).

**EXAMPLE 60:** (2*R*,3*R*,4*S*,5*R*)-2-{2-{2-[(1-Benzhydryl-3-azetidiny]amino]ethyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol

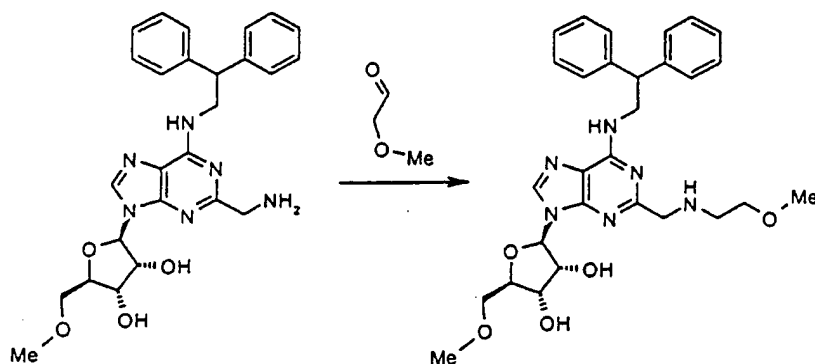


The title compound was prepared by a similar method to example 38 using 2-  
 {2-[(1-benzhydryl-3-azetidyl)amino]ethyl}-9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis[*tert*-  
 butyl(dimethyl)silyl]oxy]-5-(methoxymethyl)tetrahydro-2-furanyl]-*N*-(2,2-  
 5 diphenylethyl)-9*H*-purin-6-amine (130mg, 0.14mmol) (preparation 38) and a 1  
 molar solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (0.4ml,  
 0.4mmol). The compound was purified by column chromatography on silica gel  
 eluting with a solvent gradient of dichloromethane : methanol : ammonia (95 : 5  
 : 0.5) increasing in polarity to (90 : 10 : 1) to give the title compound (70mg) as  
 10 a foam. MS: 726 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.95 (1H, s), 7.40-7.15 (20H, m), 5.95-5.90 (1H, m), 5.70  
 (1H, s), 4.50-4.45 (1H, m), 4.40-4.30 (5H, m), 4.25 (1H, br s), 3.65-3.45 (6H,  
 m), 3.30 (3H, s), 3.00-2.90 (4H, m), 2.90-2.80 (2H, m).

15

**EXAMPLE 61:** (2*R*,3*R*,4*S*,5*R*)-2-(6-[(2,2-Diphenylethyl)amino]-2-[(2-  
 methoxyethyl)amino]methyl)-9*H*-purin-9-yl)-5-(methoxymethyl)tetrahydro-  
 3,4-furandiol



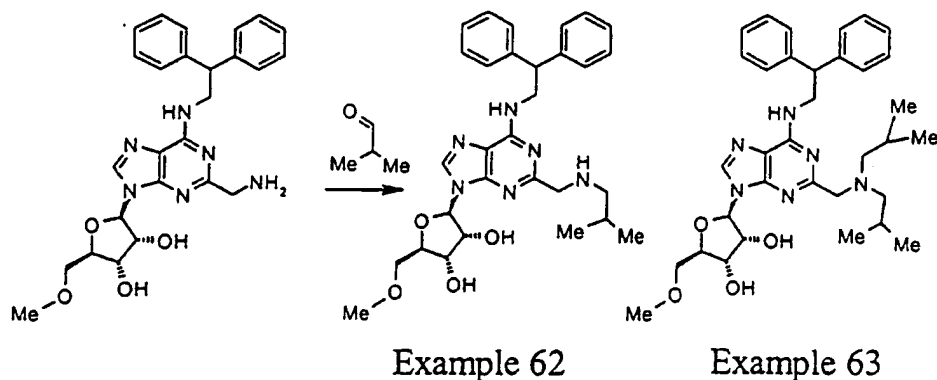
The title compound was prepared by a similar method to example 5 using (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (320mg, 0.63mmol) (example 1), 2-methoxyacetaldehyde (53mg, 0.63mmol) and sodium triacetoxyborohydride (210mg, 0.95mmol) in tetrahydrofuran (22ml). The product was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (92 : 8 : 0.4) to give the title compound (125mg) as a foam. MS: 548 (MH<sup>+</sup>).

10

<sup>1</sup>H NMR (CDCl<sub>3</sub> + trace of trifluoroacetic acid)  $\delta$  = 9.10 (1H, s), 7.35-7.20 (10H, m), 6.25-6.00 (1H, m), 4.70-4.25 (8H, m), 3.90-3.85 (1H, m), 3.85-3.75 (2H, m), 3.65-3.60 (1H, m), 3.50-3.45 (2H, m), 3.45-3.35 (6H, m).

15 **EXAMPLE 62:** (2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-Diphenylethyl)amino]-2-[(isobutylamino)methyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol and **EXAMPLE 63:** (2*R*,3*R*,4*S*,5*R*)-2-{2-[(Diisobutylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol.

20



The title compounds were prepared by a similar method to example 5 using  
 (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-  
 5-(methoxymethyl)tetrahydro-3,4-furandiol (310mg, 0.6mmol) (example 1), 2-  
 methylpropanal (44mg, 0.6 mmol) and sodium triacetoxymethylborohydride (200mg,  
 0.9mmol). The products were purified by column chromatography on silica gel  
 eluting with a solvent system of dichloromethane : methanol : ammonia (96 : 4 :  
 0.4) to give example 63 (45mg) as a foam and then with a solvent system of  
 dichloromethane : methanol : ammonia (93 : 7 : 0.3) to give example 62  
 (144mg) as a foam.

**Data for EXAMPLE 62:**

MS: 547 (MH<sup>+</sup>).

15

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.35-7.20 (10H, m), 6.00-5.95 (1H, m), 5.80  
 (1H, br s), 4.40-4.25 (6H, m), 3.90 (2H, s), 3.65-3.55 (2H, m), 3.35 (3H, s),  
 2.55-2.45 (2H, m), 1.90-1.80 (1H, m), 1.00-0.90 (6H, m).

20 Analysis : Found C, 64.13, H, 6.93, N, 14.83; C<sub>30</sub>H<sub>38</sub>N<sub>8</sub>O<sub>4</sub>·0.5H<sub>2</sub>O·0.17CH<sub>2</sub>Cl<sub>2</sub>  
 requires C, 64.08, H, 6.92, N, 14.86%.

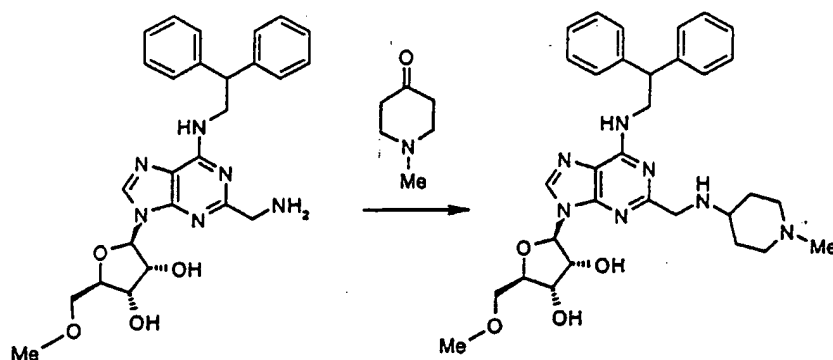
**Data for EXAMPLE 63:**

MS: 603 (MH<sup>+</sup>).

25

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 7.90 (1H, s), 7.35-7.20 (10H, m), 6.90 (1H, s), 5.85-5.75 (2H, m), 4.45-4.25 (6H, m), 3.70 (2H, s), 3.60-3.50 (2H, m), 3.30 (4H, s), 2.35-2.25 (4H, m), 1.85-1.75 (2H, m), 0.90-0.80 (12H, m).

5 **EXAMPLE 64: (2R,3R,4S,5R)-2-(6-[(2,2-Diphenylethyl)amino]-2-[(1-methyl-4-piperidiny)amino]methyl)-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydro-3,4-furandiol.**

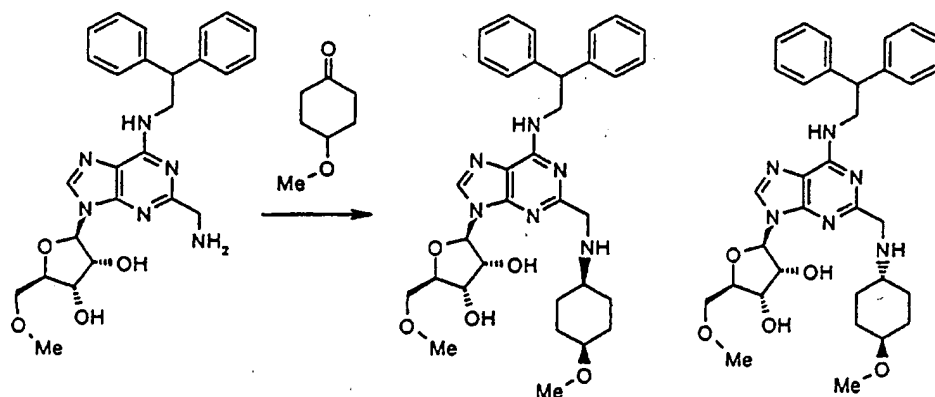


- 10 Sodium triacetoxyborohydride (162mg, 0.76mmol) was added to a stirred solution of (2R,3R,4S,5R)-2-(2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol (250mg, 0.51mmol) (example 1), 1-methyl-4-piperidinone (52mg, 0.46mmol) and acetic acid (30mg, 0.5mmol) in tetrahydrofuran (20ml). The reaction mixture was stirred for 24hr at
- 15 room temperature. The solvent was then removed under reduced pressure and the residue partitioned between dichloromethane (30ml) and saturated aqueous sodium hydrogen carbonate solution (10ml). The aqueous layer was discarded and the organic layer washed with water (10ml), separated and the solvent removed under reduced pressure to give a residue which was purified by
- 20 column chromatography on silica gel eluting with a solvent gradient of dichloromethane : methanol : ammonia (90 : 10 : 0.5) increasing in polarity to (85 : 15 : 0.75) to give the title compound contaminated with example 1. The mixture was treated with diethyl ether (10ml) and the solid filtered off. This solid was treated with diethyl ether (10ml) and then filtered. The diethyl ether filtrates

were combined and the solvent removed under reduced pressure to give the title compound (60mg) as a solid. MS: 589 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.35-7.20 (10H, m), 5.95-5.90 (1H, m), 5.85 (1H, br s), 4.45-4.20 (6H, m), 3.90 (2H, s), 3.70-3.55 (2H, m), 3.35 (3H, s), 2.90-2.80 (2H, m), 2.60-2.50 (1H, partially obscured by OH peaks, m), 2.30 (3H, s), 2.10-2.00 (2H, m), 2.00-1.80 (2H, m), 1.65-1.50 (2H, m).

**EXAMPLE 65: (2R,3R,4S,5R)-2-(6-[(2,2-Diphenylethyl)amino]-2-[(4-methoxycyclohexyl)amino]methyl)-9H-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol**



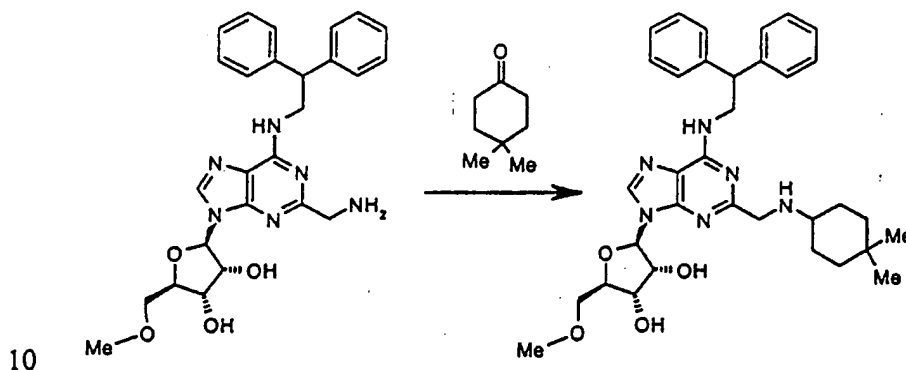
The title compound was prepared by a similar method to example 6 using (2R,3R,4S,5R)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (400mg, 0.78mmol) (example 1), sodium triacetoxymethylborohydride (260mg, 1.23mmol), 4-methoxycyclohexanone (100mg, 0.78mmol) (J. Am. Chem. Soc. 5190, 89, 1967) and acetic acid (56mg, 0.93mmol) in tetrahydrofuran (30ml). The product was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (94 : 6 : 0.3) to give the title compound as a mixture (3 : 2 ratio) of diastereoisomers (118mg) as a foam. MS: 603 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.85 (1H, s), 7.35-7.15 (10H, m), 5.95-5.90 (1H, m), 5.75 (1H, br s), 4.40-4.20 (6H, m), 3.95-3.85 (2H, m), 3.65-3.50 (2H, m), 3.35-3.25

(6.6H, m), 3.15-3.10 (0.4H, m), 2.70-2.60 (0.6H, m), 2.60-2.50 (0.4H, m), 2.05-1.95 (2H, m), 1.90-1.80 (1H, m), 1.65-1.50 (2H, m), 1.50-1.40 (1H, m), 1.25-1.15 (2H, m).

5

**EXAMPLE 66:** (2*R*,3*R*,4*S*,5*R*)-2-{2-[[4,4-Dimethylcyclohexyl]amino]methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol



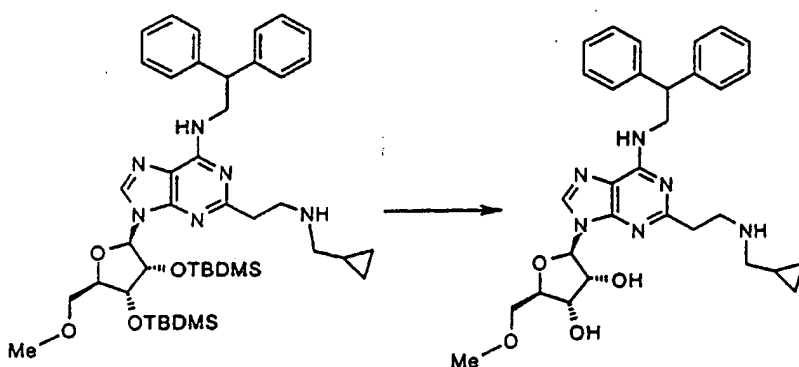
The title compound was prepared by a similar method to example 6 using (2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (330mg, 0.67mmol) (example 1), sodium triacetoxymethylborohydride (214mg, 1.01mmol), 4,4-dimethylcyclohexanone (85mg, 0.67mmol) and acetic acid (48mg, 0.80mmol) in tetrahydrofuran (30ml).  
 15 The product was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (92 : 8 : 0.4) to give the title compound (216mg) as a foam. MS: 602 (MH<sup>+</sup>).

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.35-7.20 (10H, m), 5.95-5.90 (1H, m), 5.80 (1H, br s), 4.40-4.20 (6H, m), 3.90 (2H, br s), 3.65-3.55 (2H, m), 3.30 (3H, s), 2.50-2.45 (1H, m), 1.80-1.70 (2H, m), 1.45-1.30 (4H, m), 1.20-1.10 (2H, m), 0.90-0.85 (6H, m).



Analysis : Found C, 65.94, H, 7.12, N, 13.77;  $C_{34}H_{44}N_8O_4 \cdot 0.5H_2O \cdot 0.17H_2O$   
requires C, 65.77, H, 7.32, N, 13.46%.

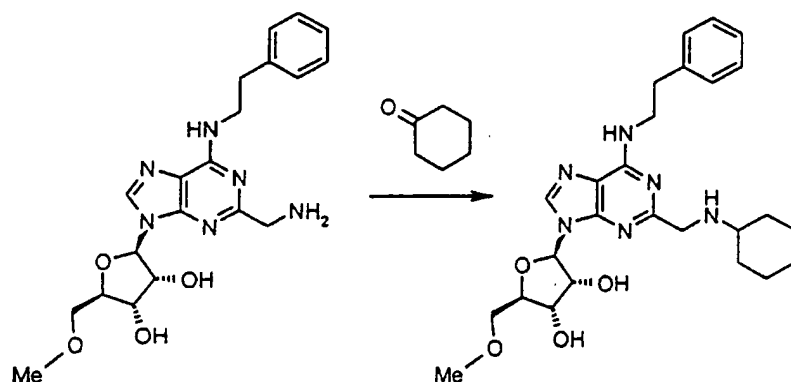
5 **EXAMPLE 67: (2R,3R,4S,5R)-2-{2-[2-[(Cyclopropylmethyl)amino]ethyl]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol**



- 10 The title compound was prepared by a similar method to example 38 using the compound of preparation 40 (190mg, 0.21mmol) and tetra-n-butyl ammonium fluoride (0.6ml of a 1 molar solution in tetrahydrofuran, 0.6mmol) in tetrahydrofuran (3ml). The product was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol (97 : 3) increasing in polarity to dichloromethane : methanol : ammonia (95 : 5 : 0.5) to  
15 give the title compound (79mg) as a foam. MS: 559 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.35-7.15 (10H, m), 5.95-5.90 (1H, m), 5.70 (1H, br s), 4.45-4.40 (1H, m), 4.40-4.30 (4H, m), 4.30-4.20 (1H, br s), 3.65-3.55 (2H, m), 3.40-3.30 (3H, s), 3.10-3.00 (2H, m), 3.00-2.95 (2H, m), 2.50-2.45 (2H, m), 0.95-0.85 (1H, m), 0.45-0.40 (2H, m), 0.10-0.05 (2H, m).  
20

**EXAMPLE 68: (2R,3R,4S,5R)-2-[2-[(Cyclohexylamino)methyl]-6-(phenethylamino)-9H-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol**



5

Sodium triacetoxyborohydride (154mg, 0.72mmol) was added to a stirred solution of (2R,3R,4S,5R)-2-[2-(aminomethyl)-6-(phenethylamino)-9H-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol (200mg, 0.48mmol) (preparation 48), acetic acid (30mg, 0.48mmol) and cyclohexanone (45mg, 0.46mmol). The reaction mixture was stirred for 24hr at room temperature and the solvent then removed under reduced pressure. The residue was then azeotroped with dichloromethane before purification by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (93 : 7 : 0.3) to give the title compound (110mg) as a viscous oil. MS: 497 (MH<sup>+</sup>).

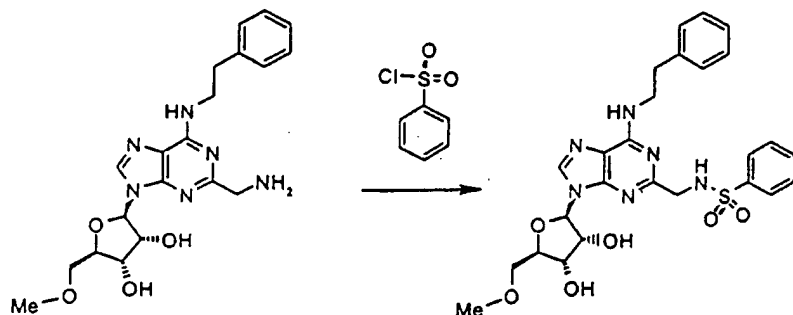
15

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.95 (1H, s), 7.35-7.20 (5H, m), 6.00-5.90 (2H, m), 4.40-4.30 (2H, m), 4.30-4.20 (1H, m), 4.00-3.85 (4H, m), 3.70-3.55 (2H, m), 3.35 (3H, s), 3.00-2.90 (2H, m), 2.60-2.50 (1H, m), 2.00-1.90 (2H, m), 1.80-1.60 (3H, m), 1.35-1.15 (5H, m).

20

Analysis : Found C, 60.88, H, 7.15, N, 16.25; C<sub>26</sub>H<sub>36</sub>N<sub>6</sub>O<sub>4</sub>·0.25H<sub>2</sub>O·0.17CH<sub>2</sub>Cl<sub>2</sub> requires C, 60.91, H, 7.19, N, 16.31%.

**EXAMPLE 69:** *N*-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-(phenethylamino)-9*H*-purin-2-yl]methyl}benzenesulfonamide



5

Phenylsulfonylchloride (57mg, 0.33mmol) was added to a stirred solution of (2*R*,3*R*,4*S*,5*R*)-2-[2-(aminomethyl)-6-(phenethylamino)-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol (150mg, 0.36mmol) (preparation 48) and triethylamine (110mg, 1.08mmol) in tetrahydrofuran (24ml). The reaction mixture was stirred for 30min at room temperature and then the solvent was removed under reduced pressure. The residue was azeotroped with dichloromethane and then purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol (95 : 5) to give the title compound (180mg) as a foam. MS: 577 (MNa<sup>+</sup>).

15

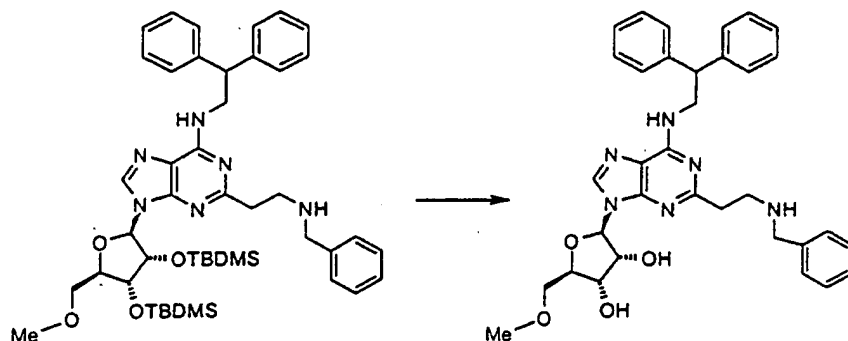
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.95 (1H, s), 7.90-7.80 (2H, m), 7.50-7.20 (8H, m), 5.95-5.85 (3H, m), 5.20 (1H, br s), 4.50 (2H, s), 4.35-4.30 (1H, m), 4.30-4.20 (2H, m), 3.85 (2H, br s), 3.70-3.55 (2H, m), 3.35 (3H, s), 3.25 (1H, s), 3.00-2.90 (2H, m).

20

Analysis : Found C, 55.06, H, 5.41, N, 14.63; C<sub>26</sub>H<sub>30</sub>N<sub>6</sub>O<sub>6</sub>S.0.17CH<sub>2</sub>Cl<sub>2</sub> requires C, 55.26, H, 5.37, N, 14.77%.

**EXAMPLE 70:** (2*R*,3*R*,4*S*,5*R*)-2-{2-[2-(Benzylamino)ethyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandi I

25

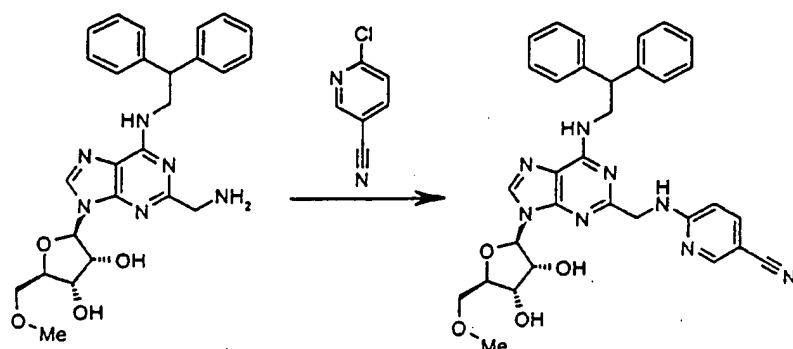


The title compound was prepared by a similar method to example 38 using *N*-benzyl-*N*-(2-{9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}ethyl)amine (360 mg, 0.44mmol) (preparation 39) and a 1 molar solution of tetrabutylammonium fluoride in tetrahydrofuran (0.92ml, 0.92mmol). The product was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane : methanol (93 : 7) increasing in polarity to dichloromethane : methanol : ammonia (90 : 10 : 1) to give the title compound (162mg) as a foam. MS: 596 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.40-7.20 (15H, m), 5.95-5.90 (1H, m), 5.75 (1H, br s), 4.40-4.15 (6H, m), 3.80 (2H, s), 3.65-3.50 (2H, m), 3.35 (3H, s), 3.15-2.95 (4H, m).

Analysis : Found C, 67.22, H, 6.57, N, 13.75; C<sub>34</sub>H<sub>38</sub>N<sub>6</sub>O<sub>4</sub>·0.67H<sub>2</sub>O requires C, 67.33, H, 6.48, N, 13.86%.

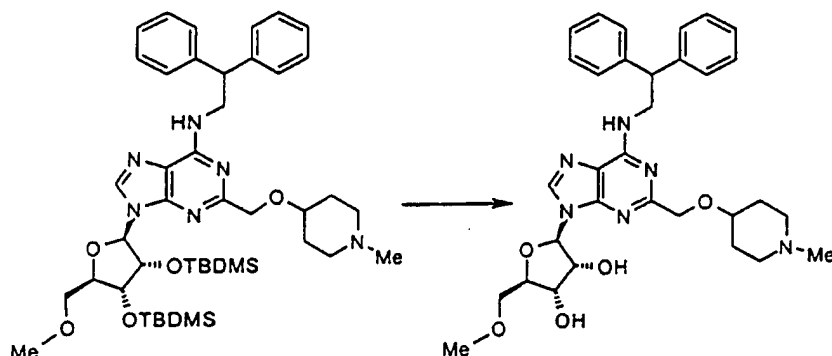
**EXAMPLE 71:** 6-[(9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl]amino]nicotinonitrile



6-Chloronicotinonitrile (78mg, 0.56mmol) was added to a stirred solution of (2R,3R,4S,5R)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol (250mg, 0.51mmol) (example 1) and triethylamine (57mg, 0.56mmol) in *N*-methyl-2-pyrrolidinone (10ml). The reaction mixture was heated at 120°C for 24hr. The reaction mixture was then partitioned between water and ethyl acetate. The ethyl acetate layer was separated, washed with brine and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a residue that was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol (95 : 5) to give material that was still impure and hence re-purified by column chromatography on silica gel eluting with a solvent system of ethyl acetate : methanol (90 : 10) to give a yellow oil which was treated with pentane to give the title compound (47mg) as a solid. MS: 594 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.40 (1H, s), 7.95 (1H, s), 7.55-7.50 (1H, m), 7.40-7.20 (10H, m), 6.45-6.40 (1H, m), 6.25 (2H, br s), 5.95-5.85 (2H, m), 5.50 (1H, br s), 4.60 (2H, br s), 4.50-4.45 (1H, m), 4.40-4.20 (5H, m), 3.65-3.55 (2H, m), 3.35 (3H, s), 3.10 (1H, s).

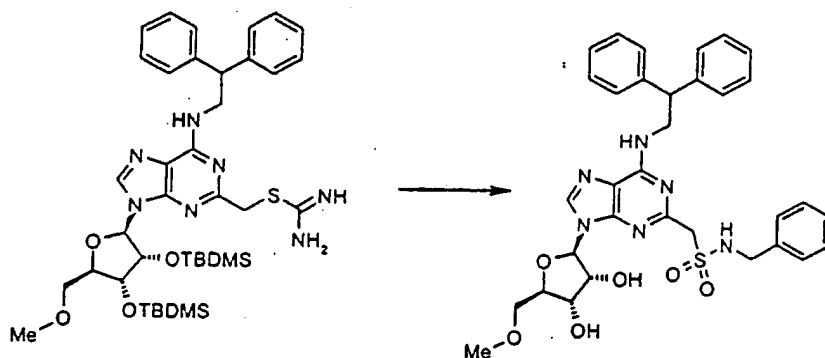
**EXAMPLE 72: (2R,3R,4S,5R)-2-(6-[(2,2-Diphenylethyl)amino]-2-[(1-methyl-4-piperidinyloxy)methyl]-9H-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol**



$N$ -(9-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-2-[[1-methyl-4-piperidinyloxy]methyl]-9*H*-purin-6-yl)- $N$ -(2,2-diphenylethyl)amine (68mg, 0.08mmol) (preparation 49) was dissolved in stirred tetrahydrofuran (10ml), then acetic acid (0.2ml, 0.2mmol) added followed by a 1 molar solution of tetra-*n*-butylammonium fluoride (0.2ml, 0.2mmol). The reaction mixture was stirred at room temperature for 1hr and then more 1 molar solution of tetrabutylammonium fluoride (0.5ml, 0.5mmol) was added. The reaction mixture was stirred for another hour and then partitioned between saturated aqueous sodium hydrogen carbonate solution and ethyl acetate. The ethyl acetate phase was separated, washed with brine and dried with anhydrous sodium sulfate. This was evaporated to give a clear oil which was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane : methanol (95 : 5) increasing in polarity to dichloromethane : methanol : ammonia (90 : 10 : 1) to give the title compound (20mg) as a foam. MS: 589 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 7.95 (1H, s), 7.40-7.15 (10H, m), 5.95-5.90 (1H, m), 5.85 (1H, br s), 4.60 (2H, s), 4.50-4.20 (8H, m), 3.65-3.55 (3H, m), 3.30 (3H, s), 2.85-2.75 (2H, m), 2.30-2.15 (5H, m), 2.05-1.95 (2H, m), 1.85-1.75 (2H, m).

**EXAMPLE 73: N-benzyl-{9-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9H-purin-2-yl}methanesulphonamide**



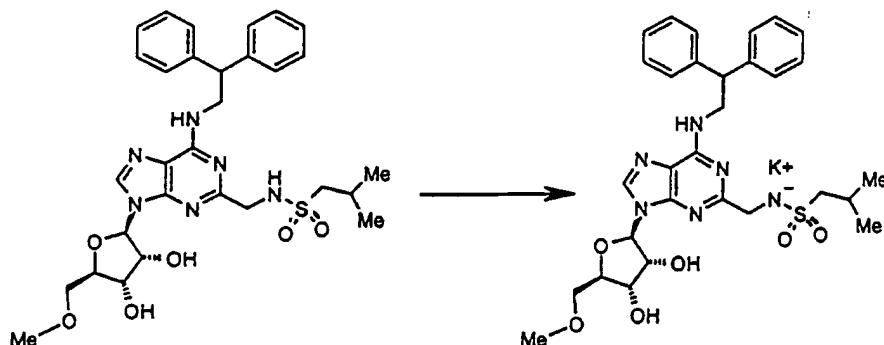
- 5 A stirred suspension of 2-({[amino(imino)methyl]sulfanyl}methyl)-9-  
 [(2R,3R,4S,5R)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-  
 diphenylethyl)amino]-9H-purine (0.75g, 0.97mmol) (preparation 50) in ice cold  
 water (20ml) was saturated with chlorine gas and stirred for 1hr. The orange  
 coloured solid that formed was filtered off, washed with water and dried. The  
 10 solid was dissolved in stirred dichloromethane (20ml), then triethylamine  
 (190mg, 1.93mmol) and benzylamine (0.16ml, 1.44mmol) were added. The  
 reaction mixture was stirred for 24hr at room temperature and then the solvent  
 was removed under reduced pressure to give a residue that was partitioned  
 between diethyl ether and 1 molar hydrochloric acid. The diethyl ether layer  
 15 was separated and the solvent removed under reduced pressure to give a solid  
 which was dissolved in stirred tetrahydrofuran and a 1 molar solution of  
 tetrabutylammonium fluoride in tetrahydrofuran (2.9ml, 2.9mmol) added. The  
 solution was stirred for 1hr and then the solvent removed under reduced  
 pressure to give a residue that was partitioned between ethyl acetate and  
 20 saturated aqueous sodium hydrogen carbonate solution. The ethyl acetate  
 layer was separated and the solvent removed under reduced pressure to give a  
 residue that was purified by column chromatography on silica gel eluting with a  
 solvent gradient of dichloromethane : methanol (97 : 3) increasing in polarity to  
 dichloromethane : methanol : ammonia (95 : 5 : 0.5). This material was re-  
 25 purified by column chromatography on silica gel eluting with a solvent gradient  
 of dichloromethane : methanol (97 : 3) increasing in polarity to dichloromethane

: methanol : ammonia (95 : 5 : 0.5) to give the title compound (63mg) as a foam. MS: 645 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.85 (1H, br s), 7.40-7.20 (15H, m), 5.90-5.80 (2H, m),  
 5 4.55-4.15 (10H, m), 3.65-3.50 (2H, m), 3.35-3.25 (3H, m).

Analysis : Found C, 60.37, H, 5.62, N, 12.74; C<sub>33</sub>H<sub>36</sub>N<sub>6</sub>O<sub>6</sub>S.0.66H<sub>2</sub>O requires C, 60.36, H, 5.68, N, 12.80%.

- 10 **Example 74: Potassium *N*-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl)-2-methyl-1-propanesulfamate.**



- 15 *N*-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl)-2-methyl-1-propanesulfonamide (example 15) (1.9g, 3.11mmol) was dissolved into isopropyl alcohol (20ml) and a 4 molar solution of potassium hydroxide (0.9ml, 3.11mmol) added. The isopropyl alcohol was removed by evaporation under reduced pressure and more isopropyl alcohol (20ml) added to the residue, then  
 20 the solvent removed under reduced pressure again. The residue was suspended in isopropyl alcohol (160ml) and then the suspension heated under reflux for 1hr. The resulting suspension was allowed to cool and then filtered. The white solid was washed with a little isopropyl alcohol and then dried. This gave the title compound (1.5g) as a white crystalline solid m.p. 231°C.



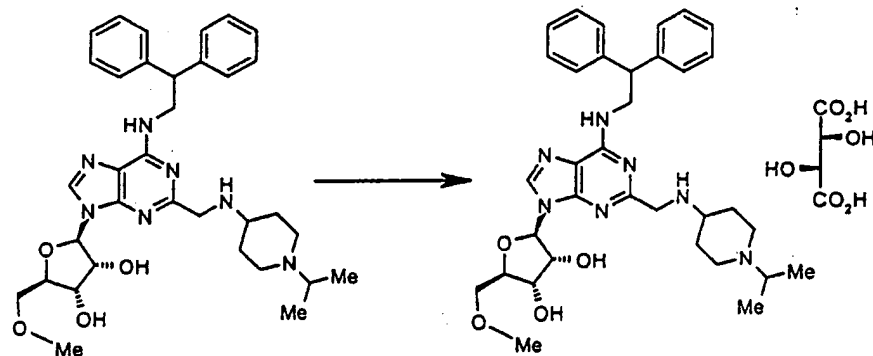
$^1\text{H}$  NMR ( $d_6$  DMSO)  $\delta$  = 8.05 (1H, s), 7.35-7.20 (8H, m), 7.20-7.10 (2H, m), 5.95-5.85 (1H, m), 4.65-3.90 (11H possibly HOD in DMSO, m), 3.60-3.40 (2H, m), 3.25 (3H, s), 2.55 (2H partly obscured by  $D_5H$  DMSO), 2.05-1.90 (1H, m), 0.90-0.80 (6H, m).

5

Analysis : Found C, 54.62, H, 5.75, N, 12.56;  $C_{30}H_{37}N_6O_6SK.0.5H_2O$  requires C, 54.78, H, 5.82, N, 12.78%.

**EXAMPLE 75: (2R,3R,4S,5R)-2-(6-[(2,2-Diphenylethyl)amino]-2-[[1-isopropyl-4-piperidinyl)amino]methyl]-9H-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol (2S,3S)-2,3-dihydroxybutanedioate**

10



A solution of (2S,3S)-2,3-dihydroxybutanedioic acid (49mg, 0.33mmol) in isopropyl alcohol (1ml) was added to a stirred solution of ((2R,3R,4S,5R)-2-(6-[(2,2-diphenylethyl)amino]-2-[[1-isopropyl-4-piperidinyl)amino]methyl]-9H-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol (200mg, 0.33mmol) (example 16) in isopropyl alcohol (1ml). This resulted in the formation of a thick precipitate, which was dissolved by the addition of dichloromethane and isopropyl alcohol. The solvent was boiled off from the solution until a gum started to appear and then more isopropyl alcohol was added. The resulting white crystalline solid was filtered off, dried and then recrystallized from hot ethanol to give the title compound (40mg) as a white powder. M.p. 161-163°C.

20

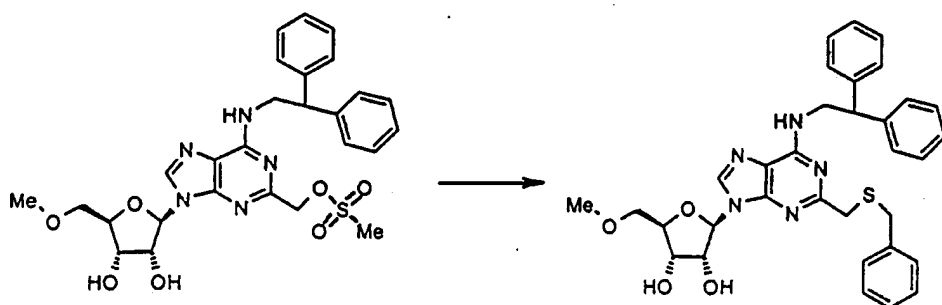
<sup>1</sup>H NMR (d<sub>6</sub> DMSO) δ = 8.25 (1H, s), 7.90 (1H, s), 7.35-7.20 (8H, m), 7.20-7.10 (2H, m), 5.95-5.85 (1H, m), 4.65-4.50 (2H, m), 4.15-4.05 (2H, m), 4.05-3.95 (2H, m), 3.85 (2H, s), 3.60-3.45 (2H, m), 3.25 (3H, s), 3.05-2.85 (4H, m), 2.45-2.30 (2H, m), 2.05-1.90 (2H, m), 1.65-1.45 (2H, m), 1.05-0.95 (6H, m).

5

Analysis : Found C, 58.06, H, 6.82, N, 12.31; C<sub>34</sub>H<sub>43</sub>N<sub>7</sub>O<sub>4</sub>·C<sub>4</sub>H<sub>6</sub>O<sub>6</sub>·H<sub>2</sub>O requires C, 58.23, H, 6.82, N, 12.51%.

**EXAMPLE 76: (2*R*,3*R*,4*S*,5*R*)-2-{2-[(Benzylsulfanyl)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol.**

10



15 {9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl methanesulfonate (300mg, 0.53mmol) (preparation 25) was dissolved in stirred dichloromethane (4ml) and phenylmethanethiol (0.13ml, 1.05mmol) and triethylamine (0.15ml, 1.05mmol) added. The reaction mixture was stirred for 48hr at room temperature and then

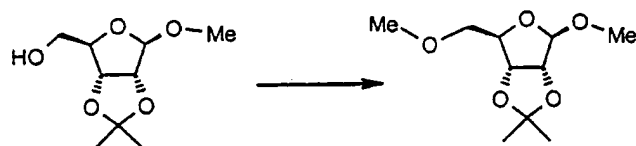
20 the solvent removed under reduced pressure. The residue was partitioned between methanol (100ml) and hexane (100ml) and the methanol layer washed with a further amount of hexane (100ml). The solvent was then removed under reduced pressure from the methanol layer. The residue was purified by column chromatography on silica gel eluting with a solvent system of ethyl acetate :

25 hexane (3 : 2) increasing in polarity to ethyl acetate : methanol (98 : 2). This gave title compound (100 mg) as a foam. MS: 599 (MH<sup>+</sup>).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 7.90 (1H, s), 7.35-7.10 (15H, m), 6.30 (1H, br s), 5.95-5.85 (2H, m), 4.50-4.25 (6H, m), 3.80 (2H, s), 3.75 (2H, s), 3.65-3.50 (2H, m), 3.45 (1H, br s), 3.30 (3H, s).

The following Preparations illustrate the preparation of certain starting materials used in the preceding Examples.

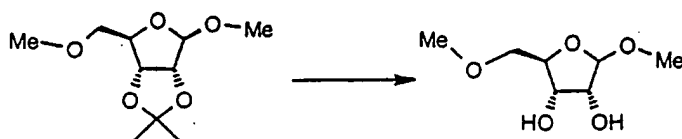
**PREPARATION 1: (3a*R*,4*R*,6*R*,6a*R*)-4-Methoxy-6-(methoxymethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole**



A stirred solution of [(3a*R*,4*R*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]methanol (J. Heterocycl. Chem., 13, 1966, 485) (43.1g, 0.21mol) in dry tetrahydrofuran (400ml), at 0°C and under an atmosphere of nitrogen, was carefully treated with sodium hydride, (7.7g of an 80% dispersion in mineral oil, 0.26mol). The resultant mixture was warmed to room temperature and stirred for 1hr. The reaction mixture was cooled to 0°C and a solution of methyl iodide (15.8ml, 0.25mol) in dry tetrahydrofuran (30ml) added slowly. The resultant mixture was stirred for a further 30min at 0°C and then at room temperature for 24hr. Water (1000ml) was added carefully and the mixture extracted with diethyl ether (3x500ml). The combined organic extracts were washed with brine, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent system of diethyl ether : pentane (1 : 4), to afford the title compound as an oil (36.5g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 4.95 (1H, s), 4.65 (1H, d), 4.55 (1H, d), 4.30 (1H, t), 3.45-3.35 (5H, m), 3.30 (3H, s), 1.45 (3H, s), 1.30 (3H, s).

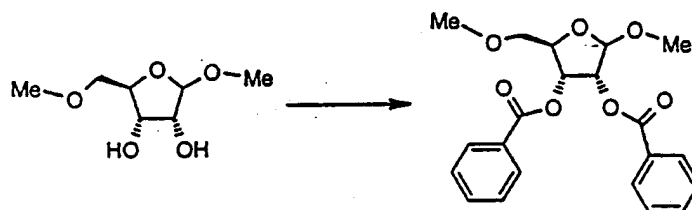
**PREPARATION 2: (2*R*,3*R*,4*S*,5*R*)-2-Methoxy-5-(methoxymethyl)tetrahydro-3,4-furandiol and (2*S*,3*R*,4*S*,5*R*)-2-methoxy-5-(methoxymethyl)tetrahydro-3,4-furandiol**



A stirred solution of (3aR,4R,6R,6aR)-4-methoxy-6-(methoxymethyl)-2,2-dimethyl tetrahydrofuro[3,4-d][1,3]dioxole (preparation 1) (36.5g, 0.17mol) in methanol (180ml) at 0°C was treated with 2 molar hydrochloric acid (180ml) and stirred at room temperature for 24hr. Solid sodium hydrogen carbonate (40g) was added portion wise to neutralise the solution (pH 7) before solvent removal under reduced pressure. The residue was dissolved in dichloromethane and the solution dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to afford the title compound as an oil and as a mixture of anomers (25.7g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 4.95 (0.25H, d), 4.85 (0.75H, d), 4.20 (0.75H, m), 4.15-4.00, (2H, m), 3.95 (0.25H, m), 3.60-3.45 (3H, m), 3.45-3.30 (5H, m), 2.85 (0.25H, d), 2.60 (1H, m), 2.45 (0.75H, d).

**PREPARATION 3: (2R,3R,4R,5R)-4-(Benzoyloxy)-5-methoxy-2-(methoxymethyl)tetrahydro-3-furanyl benzoate and (2R,3R,4R,5S)-4-(benzoyloxy)-5-methoxy-2-(methoxymethyl)tetrahydro-3-furanyl benzoate**

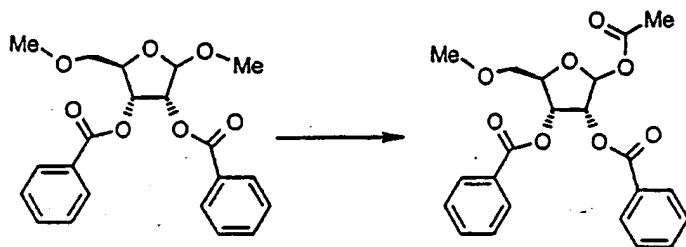


A stirred solution of (2R,3R,4S,5R)-2-methoxy-5-(methoxymethyl)tetrahydro-3,4-furandiol and (2S,3R,4S,5R)-2-methoxy-5-(methoxymethyl)tetrahydro-3,4-furandiol (preparation 2) (25.7g, 0.14mol) and pyridine (44ml, 0.54mol) in dry dichloromethane (350ml) was treated with benzoyl chloride (40ml, 0.34mol) at 0°C and the resultant mixture then stirred at room temperature for 24hr. The solvent was removed under reduced pressure and the residue partitioned between diethyl ether and water. The layers were then separated and the

aqueous layer extracted with diethyl ether : pentane (1 : 1). The combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient  
 5 system of dichloromethane : diethyl ether (9 : 1) gradually changing to dichloromethane : diethyl ether (4 : 1) to afford the title compound as an oil and as a mixture of anomers (54.5g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 8.05 (0.75H, d), 8.00 (1.25H, d), 7.95 (2H, dd), 7.60-7.20, (6H, m), 5.65-5.58 (1.75H, m), 5.40 (0.25H, d), 5.30-5.22 (0.25H, m), 5.15 (0.75H, s), 4.58-4.50 (0.75H, m), 4.45 (0.25H, m), 3.75-3.70 (1.25H, m), 3.70-3.60 (0.75H, m), 3.50-3.40 (6H, m).

**PREPARATION 4: (2*R*,3*R*,4*R*,5*S*)-5-(Acetyloxy)-4-(benzoyloxy)-2-(methoxymethyl)tetrahydro-3-furanyl benzoate and (2*R*,3*R*,4*R*,5*R*)-5-(acetyloxy)-4-(benzoyloxy)-2-(methoxymethyl)tetrahydro-3-furanyl benzoate**



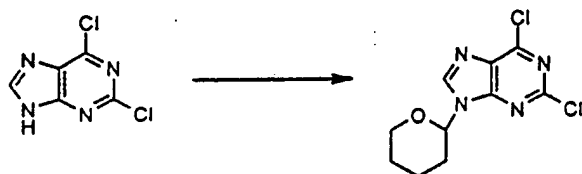
A stirred solution of (2*R*,3*R*,4*R*,5*R*)-4-(benzoyloxy)-5-methoxy-2-(methoxymethyl)tetrahydro-3-furanyl benzoate and (2*R*,3*R*,4*R*,5*S*)-4-(benzoyloxy)-5-methoxy-2-(methoxymethyl) tetrahydro-3-furanyl benzoate (preparation 3) (53.2g, 0.14mol) in dichloromethane (600ml) at 0°C was treated slowly with acetic anhydride (34ml, 0.36mol), acetic acid (16.5ml, 0.29mol) and concentrated sulphuric acid (1ml, 18.8mmol). The resultant mixture was stirred  
 25 at room temperature for 24hr. The reaction mixture was then diluted with water (1000ml), solid sodium hydrogen carbonate (80g) added portion wise to neutralise the solution (pH 7) and the mixture stirred for a further 2hr. Dichloromethane (500ml) and water (500ml) were added to the reaction mixture

and the layers were separated. The aqueous layer was then extracted with dichloromethane, and the combined organic layers washed with brine, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to afford the title compound as an oil and as a mixture of anomers (57.5g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 8.10 (1H, d), 8.00 (1H, d), 7.95-7.80 (2H, m), 7.60-7.25, (6H, m), 6.65 (0.5H, s), 6.40, (0.5H, s), 5.80-5.70 (1.5H, m), 5.55 (0.5H, m), 4.60 (1H, m), 3.80-3.60 (2H, m), 3.45 (3H, d), 2.15 (1.5H, s), 2.10 (1.5H, s).

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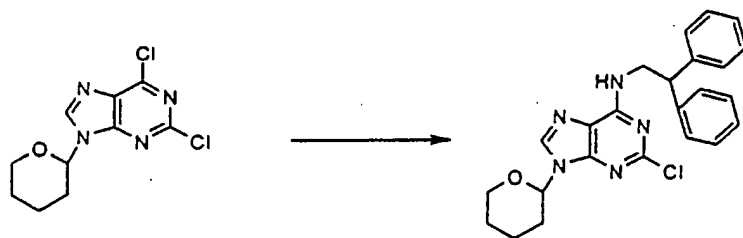
#### PREPARATION 5: 2,6-Dichloro-9-tetrahydro-2H-pyran-2-yl-9H-purine



2,6-Dichloro-9H-purine (20g, 0.11mol) and 4-toluenesulphonic acid monohydrate (0.2g) were dissolved in stirred ethyl acetate (300ml), the mixture heated to 50°C and a solution of 2,3-dihydropyran (12.6ml, 0.14mol) in ethyl acetate (50ml) added slowly over 30min. The reaction mixture was then cooled to room temperature and water (100ml) added and the pH of the solution adjusted to 7 with a saturated aqueous solution of sodium hydrogen carbonate. The layers were separated and the organic layer washed sequentially with water and brine, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was dissolved in pentane and the solvent removed under reduced pressure again. This was then repeated, to afford the title compound as a slightly impure white solid (30.9g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 8.30 (1H, s), 5.75 (1H, dd), 4.25-4.15 (1H, m), 3.85-3.70 (1H, m), 2.20-1.60 (6H, m).

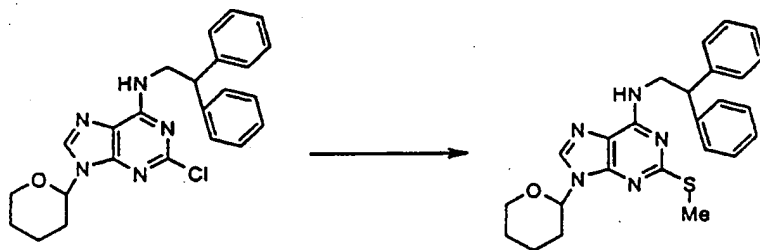
#### PREPARATION 6: 2-Chloro-N-(2,2-diphenylethyl)-9-tetrahydro-2H-pyran-2-yl-9H-purin-6-amine



A stirred solution of 2,6-dichloro-9-tetrahydro-2H-pyran-2-yl-9H-purine (preparation 5) (30.9g, 0.11mol) in isopropyl alcohol (600ml) was treated with *N*-ethyl-*N*-isopropyl-2-propanamine (47.5ml, 0.27mol) and 2,2-diphenylethylamine (24.8g, 0.13mol) and the resulting mixture heated at reflux for 3hr. The solvent was removed under reduced pressure, the residue dissolved in ethyl acetate and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of ethyl acetate : hexane (40 : 60) gradually changing to ethyl acetate : hexane (60 : 40) to afford the title compound as a foam (49.7g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  = 7.95-7.75 (1H, br s), 7.35-7.15 (10H, m), 5.80-5.70 (1H, br s), 5.65 (1H, d), 4.35 (1H, m), 4.30-4.18 (1H, br s), 4.10 (1H, d), 3.70 (1H, t), 2.05-1.95 (2H, m), 1.95-1.80 (1H, m), 1.80-1.55 (3H, m).

**PREPARATION 7: *N*-(2,2-Diphenylethyl)-2-(methylsulfanyl)-9-tetrahydro-2H-pyran-2-yl-9H-purin-6-amine**



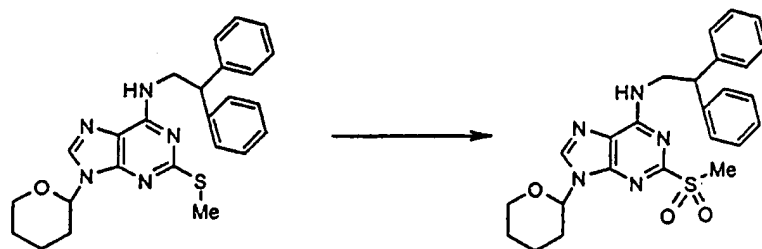
A stirred solution of 2-chloro-*N*-(2,2-diphenylethyl)-9-tetrahydro-2H-pyran-2-yl-9H-purin-6-amine (preparation 6) (49.7g, 0.11mol) in dry *N,N*-dimethylformamide (200ml) was treated with sodium thiomethoxide (10g, 0.14mol) and the resulting mixture heated under an atmosphere of nitrogen at 100°C for 1.5hr. The mixture was then stirred at room temperature for 72hr and



then reheated to 100°C for a further 2hr. The reaction mixture was then cooled and diluted with water (1000ml). A suspension was formed which was extracted with diethyl ether (x2). The combined organic extracts were washed sequentially with water and brine, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was dissolved in diethyl ether and the solvent removed under reduced pressure. This procedure was then repeated using pentane to afford the title compound as a foam (48.9g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 7.80 (1H, s), 7.20-7.10 (10H, m), 5.70-5.55 (2H, d), 4.40-4.20 (3H, m), 4.20-4.05 (1H, m), 3.80-3.65 (1H, m), 2.60 (3H, s), 2.15-1.90 (3H, m), 1.90-1.60 (3H, m).

**PREPARATION 8: *N*-(2,2-Diphenylethyl)-2-(methylsulfonyl)-9-tetrahydro-2H-pyran-2-yl-9H-purin-6-amine**

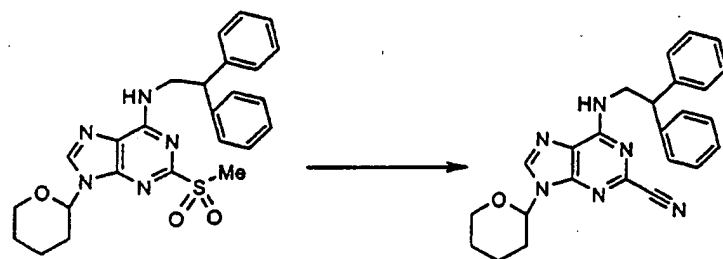


A solution of oxone<sup>®</sup> (potassium peroxymonosulphate) (44g, 71.7mmol) in water (200ml) was added drop wise over 2hr to a stirred solution of *N*-(2,2-diphenylethyl)-2-(methylsulfanyl)-9-tetrahydro-2H-pyran-2-yl-9H-purin-6-amine (preparation 7) (25g, 56.2mmol) and sodium hydrogen carbonate (20g, 238mmol) in acetone (1000ml) and water (250ml). The resultant mixture was stirred at room temperature for 24hr, filtered and the residue washed with acetone. The acetone was removed from the filtrate under reduced pressure and the resulting aqueous residue extracted with ethyl acetate and then dichloromethane. The combined organic extracts were washed with brine, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was triturated with diethyl ether, the

mixture filtered and the collected material washed with diethyl ether and pentane, then dried to afford the title compound as a white solid (20.32g).

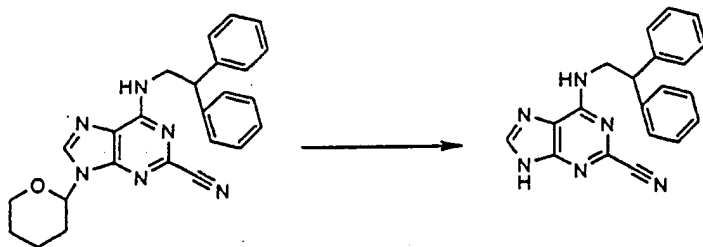
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 8.00 (1H, s), 7.35-7.15 (10H, m), 6.05-5.95 (1H, br s), 5.75 (1H, d), 4.40-4.35 (1H, m), 4.35-4.20 (2H, br s), 4.15-4.05 (1H, m), 3.75 (1H, t), 3.30 (3H, s), 2.18-2.05 (1H, m), 2.05-1.98 (1H, m), 1.98-1.80 (1H, m), 1.80-1.60 (3H, m).

**PREPARATION 9: 6-[(2,2-Diphenylethyl)amino]-9-tetrahydro-2H-pyran-2-yl-9H-purine-2-carbonitrile**



A stirred solution of *N*-(2,2-diphenylethyl)-2-(methylsulfonyl)-9-tetrahydro-2H-pyran-2-yl-9H-purin-6-amine (preparation 8) (20.1g, 42.1mmol) in dry *N,N*-dimethylformamide (100ml) was treated with potassium cyanide (5.5g, 84.6mmol) and the mixture heated at 120°C for 24hr under a nitrogen atmosphere. The mixture was then cooled to room temperature, poured into water (1000ml) and stirring continued for a further 1hr. The resultant solid was slowly filtered and washed several times with water, then dissolved in dichloromethane. The solution washed with water, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was then dissolved in diethyl ether and the solvent removed under reduced pressure (repeated) to afford the title compound as an oil (17g).

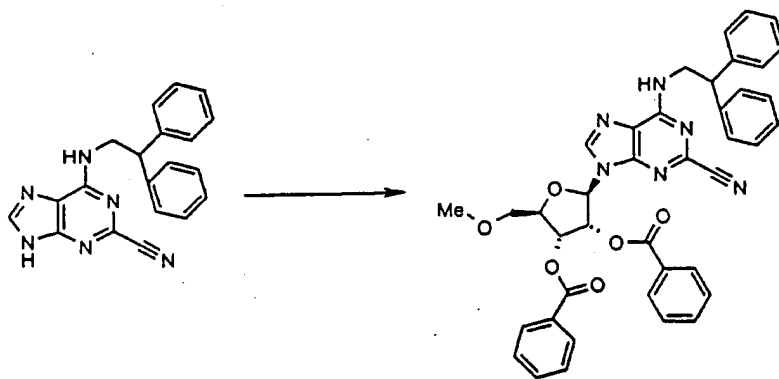
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 8.00 (1H, s), 7.40-7.20 (10H, m), 6.00-5.75 (1H, br s), 5.70 (1H, d), 4.40-4.20 (3H, m), 4.20-4.10 (1H, m), 3.80-3.70 (1H, m), 2.20-1.90 (3H, m), 1.90-1.60 (3H, m).

**PREPARATION 10: 6-[(2,2-Diphenylethyl)amino]-9H-purine-2-carbonitrile**

A stirred solution of 6-[(2,2-diphenylethyl)amino]-9-tetrahydro-2H-pyran-2-yl-9H-purine-2-carbonitrile (preparation 9) (17g, 40.1mmol) in ethanol (850ml), was  
 5 treated with 2 molar hydrochloric acid (50ml) and the mixture stirred at room temperature for 24hr. The solvent was then removed under reduced pressure, the residue dissolved in ethanol and the solvent removed under reduced pressure (repeated). The residue was triturated with diethyl ether, the mixture filtered and the collected material washed with diethyl ether and pentane, then  
 10 dried to afford the title compound as a solid (14.3g). MS: 341 (MH<sup>+</sup>)

<sup>1</sup>H-NMR (d<sub>6</sub> DMSO) δ = 8.30 (1H, s), 8.20-8.05 (1H, br s), 7.40-7.10 (10H, m), 4.60-4.40 (1.4H, m), 4.20-4.00 (1.6H, m).

Analysis : Found C, 70.37, H, 4.70, N, 24.58; C<sub>20</sub>H<sub>16</sub>N<sub>6</sub>. requires C, 70.57, H, 4.74, N, 24.69%.

**PREPARATION 11: (2R,3R,4R,5R)-4-(benzoyloxy)-5-{2-cyano-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl}-2-(methoxymethyl)tetrahydro-3-furanyl benzoate**

A stirred mixture of 6-[(2,2-diphenylethyl)amino]-9*H*-purine-2-carbonitrile (preparation 10) (5g, 14.7mmol), ammonium sulphate (200mg, 1.8mmol) and 1,1,1,3,3,3-hexamethyldisilazane (100ml) was heated at 130°C for 24hr. Further portions of ammonium sulphate (200mg, 1.8mmol) and 1,1,1,3,3,3-hexamethyldisilazane (100ml) were then added and the mixture heated at 130°C for a further 4hr. The solvent was then removed under reduced pressure and the residue dissolved in acetonitrile. The solvent was again removed under reduced pressure and the residue redissolved in acetonitrile (10ml) to give solution A.

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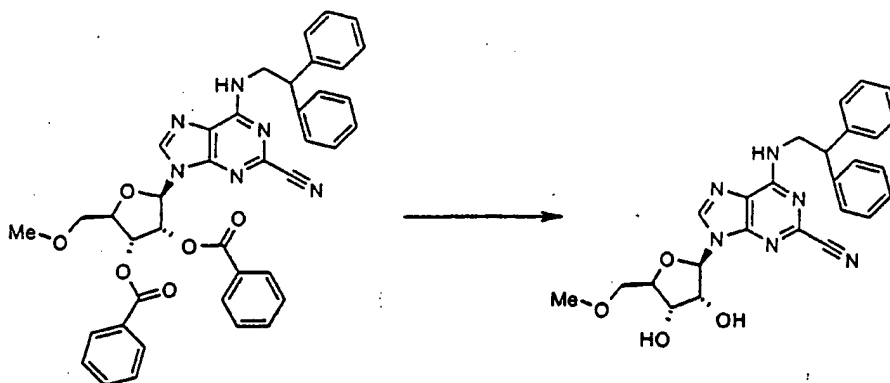
In a separate reaction vessel, a stirred solution of (2*R*,3*R*,4*R*,5*S*)-5-(acetyloxy)-4-(benzoyloxy)-2-(methoxymethyl)tetrahydro-3-furanyl benzoate and (2*R*,3*R*,4*R*,5*R*)-5-(acetyloxy)-4-(benzoyloxy)-2-(methoxymethyl)tetrahydro-3-furanyl benzoate (preparation 4) (6.2g, 14.9mmol) and bismuth tribromide (350mg, 0.78mmol) in dichloromethane (100ml) was treated with bromotrimethylsilane (8ml, 60.6mmol) under an atmosphere of nitrogen and the mixture stirred at room temperature for 10min. The solvent was removed under reduced pressure and the residue dissolved in acetonitrile. The solvent was again removed under reduced pressure and the residue redissolved in acetonitrile (10ml) to give solution B. Solution A was then added to stirred solution B and the mixture stirred at room temperature for 24hr. The mixture was then partitioned between saturated aqueous sodium hydrogen carbonate and ethyl acetate. The layers were separated and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of ethyl acetate : pentane (2 : 3) gradually changing to ethyl acetate : pentane (2 : 1) to afford the title compound as a white foam (6.26g). MS: 695 (MH<sup>+</sup>)

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<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 8.35 (1H, s), 8.05 (2H, d), 7.95 (2H, d), 7.65-7.20 (16H, m), 6.60 (1H, d), 6.05-5.90 (3H, m), 4.60 (1H, s), 4.40-4.20 (3H, m), 3.80 (2H,

s), 3.55 (3H, s).

**PREPARATION 12: 9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purine-2-carbonitrile**

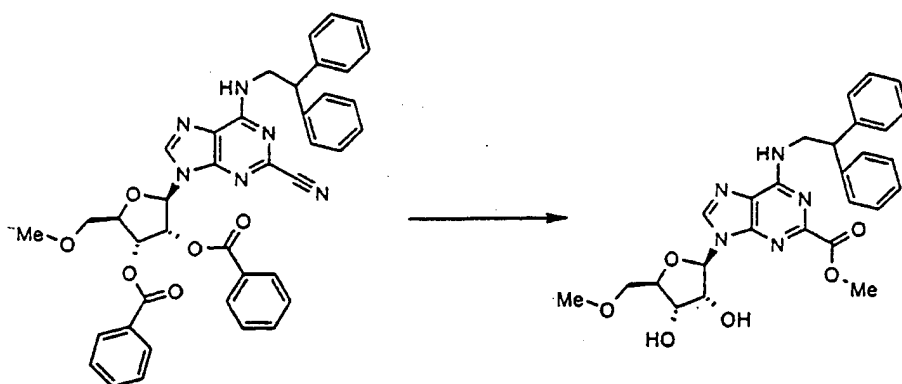


A solution of (2*R*,3*R*,4*R*,5*R*)-4-(benzoyloxy)-5-{2-cyano-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-2-(methoxymethyl)tetrahydro-3-furanyl benzoate (preparation 11) (6.75g, 9.72mmol) in methanol (300ml) saturated with ammonia gas was stirred at room temperature for 72hr. The solvent was removed under reduced pressure, the residue dissolved in dichloromethane and the solvent removed under reduced pressure (repeated). The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol (98 : 2) gradually changing to dichloromethane : methanol (96 : 4). The residue was triturated with diethyl ether, filtered, washed with diethyl ether and dried to afford the title compound as a solid (2.20g). MS: 487(MH<sup>+</sup>)

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 8.15 (1H, s), 7.40-7.20 (10H, m), 6.05 (1H, br s), 6.00 (1H, d), 4.60 (1H, m), 4.45 (1H, m), 4.40-4.20 (4H, m), 3.75-3.55 (2H, m), 3.40 (3H, s), 3.00 (1H, m).

Analysis : Found C, 63.84, H, 5.22, N, 17.16; C<sub>26</sub>H<sub>28</sub>N<sub>6</sub>O<sub>4</sub> requires C, 64.19, H, 5.39, N, 17.27%.

**PREPARATION 13: Methyl 9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purine-2-carboxylate**

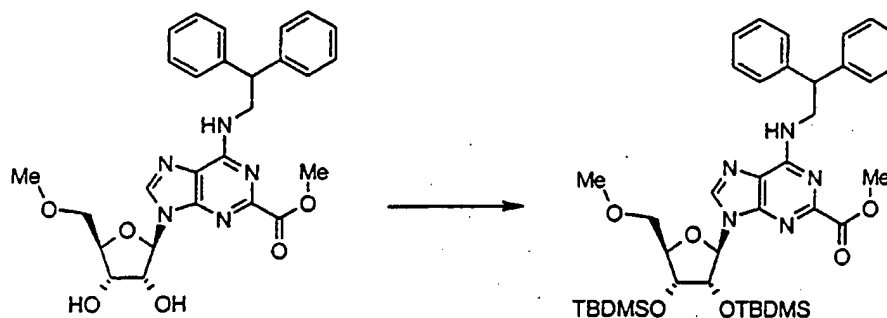


- 5 Sodium methoxide (0.69g, 12.7mmol) was added to a stirred solution of (2*R*,3*R*,4*R*,5*R*)-4-(benzoyloxy)-5-{2-cyano-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-2-(methoxymethyl) tetrahydro-3-furanyl benzoate (8.85g, 12.7mmol) (preparation 11) in methanol (150ml) and the mixture stirred at 60°C, under a nitrogen atmosphere, for 3hr. The solvent was removed under reduced
- 10 pressure and tetrahydrofuran (80ml) and 2 molar hydrochloric acid (50ml) added. The mixture was stirred for 90 minutes before carefully adding solid sodium hydrogen carbonate (~9g) to neutralise the solution (pH 7). The resulting mixture was then partitioned between ethyl acetate and water, the aqueous layer separated and extracted with more ethyl acetate. The combined
- 15 organic solutions were washed with brine and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a gradient system of ethyl acetate changing to ethyl acetate : methanol (95 : 5) to afford the title compound as a foam (4.55g).

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<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 8.19 (1H, s), 7.20-7.38 (10H, m), 6.27 (1H, d), 5.99 (1H, br s), 5.89 (1H, br s), 4.30-4.60 (5H, m), 4.06 (1H, s), 3.95 (3H, s), 3.64 (2H, dd), 3.38 (3H, s).

**PREPARATION 14: Methyl 9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis[[*tert*-butyl(dimethyl)silyl]oxy]-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purine-2-carboxylate**

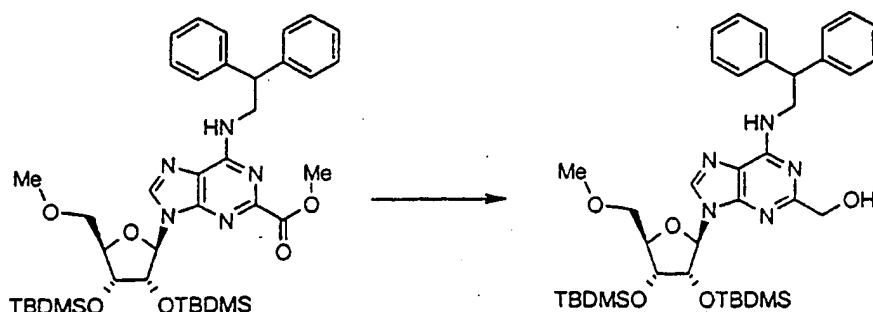


- 5 Methyl 9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purine-2-carboxylate, (1.48g, 3mmol) (preparation 13), imidazole (0.82g, 12mmol) and *tert*-butyl(chloro)dimethylsilane (1.36g, 9mmol) were dissolved in anhydrous *N,N*-dimethylformamide (15ml) and the solution stirred at room temperature for 18hr. The resulting mixture was
- 10 then partitioned between ethyl acetate and water, the organic phase washed with brine and the combined organic solutions dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a gradient system of hexane : ethyl acetate (13 : 1) changing to hexane : ethyl acetate (2 : 1) to
- 15 afford the title compound as an oil (1.52g). MS: 749 (MH<sup>+</sup>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 8.36 (1H, s), 7.18-7.38 (10H, m), 6.03 (1H, d), 5.98 (1H, br s), 4.20-4.50 (5H, m), 3.99 (3H, s), 3.83 (1H, dd), 3.62 (1H, dd), 3.43 (3H, s), 0.89 (18H, d), 0.02-0.13 (12H, m).

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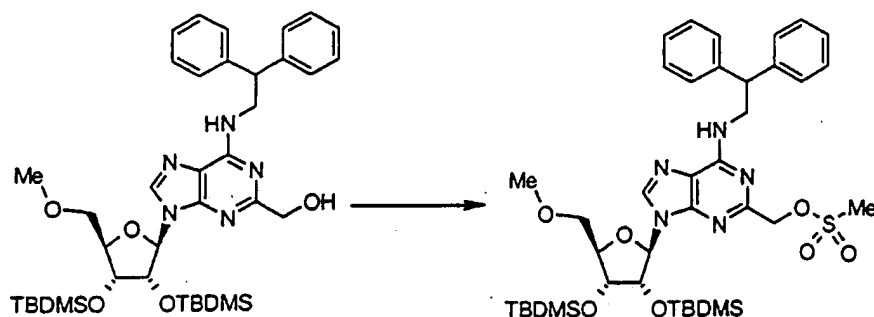
**PREPARATION 15: {9-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis[[*tert*-butyl(dimethyl)silyl]oxy]-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amin ]-9*H*-purin-2-yl}methanol**



- A stirred solution of methyl 9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis[[*tert*-butyl(dimethyl)silyl]oxy]-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purine-2-carboxylate (7.2g, 9.64mmol) (preparation 14) in dry diethyl ether (150ml) was treated with trimethyl borate (0.11ml, 0.97mmol) and lithium borohydride (212mg, 9.64mmol) and the mixture heated at reflux for 1hr under a nitrogen atmosphere. The mixture was then cooled to room temperature, water (100ml) carefully added and stirring continued for 10 minutes. The organic phase was separated, washed with brine and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a gradient system of diethyl ether : pentane (1 : 1) changing to diethyl ether : pentane (3 : 1) to afford the title compound as an oil (5.17g). MS: 721 (MH<sup>+</sup>).
- <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 8.19 (1H, s), 7.20-7.36 (10H, m), 5.95 (1H, d), 5.85 (1H, br s), 4.69 (2H, s), 4.15-4.50 (6H, m), 3.75-3.87 (2H, m), 3.59 (1H, dd), 3.42 (3H, s), 0.91 (9H, s), 0.87 (9H, s), 0.01-0.12 (12H, m).

- PREPARATION 16:** {9-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis[[*tert*-butyl(dimethyl)silyl]oxy]-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl methanesulfonate

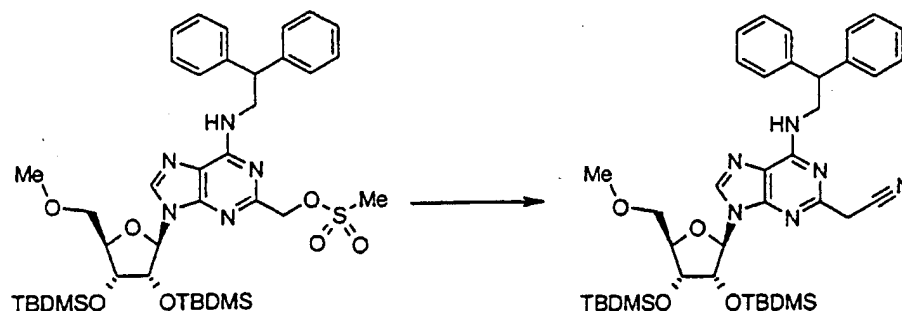




Methanesulfonyl chloride (0.6ml, 7.7mmol) was slowly added to a stirred solution of {9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis[[*tert*-butyl(dimethyl)silyl]oxy]-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methanol (4.22g, 5.87mmol) (preparation 15) and triethylamine (1.2ml, 8.62mmol) in dichloromethane (50ml) and the mixture stirred at room temperature for 30 minutes. Triethylamine (1ml, 7.2mmol) and methanesulfonyl chloride (0.5ml, 6.4mmol) were then added and stirring continued for a further 15 minutes. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a gradient system of ethyl acetate : pentane (1 : 3) changing to ethyl acetate : pentane (1 : 1) to afford the title compound as a gum (4.52g). MS: 820 (MNa<sup>+</sup>).

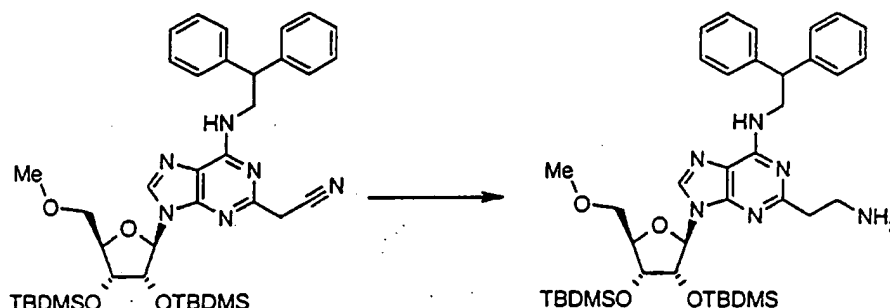
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 8.20 (1H, s), 7.20-7.46 (10H, m), 5.96 (1H, d), 5.70 (1H, br s), 5.25 (2H, s), 4.50 (1H, t), 4.17-4.40 (4H, m), 3.79 (1H, dd), 3.60 (1H, dd), 3.44 (3H, s), 3.10 (3H, s), 0.92 (9H, s), 0.86 (9H, s), 0.01-0.10 (12H, m).

**PREPARATION 17: 2-{9-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis[[*tert*-butyl(dimethyl)silyl]oxy]-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}acetonitrile**



- A stirred solution of {9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis[[*tert*-butyl(dimethyl)silyl]oxy]-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl methanesulfonate (3.0g, 3.76mmol) (preparation 16) in anhydrous
- 5 *N,N*-dimethylformamide (20ml) was treated with potassium cyanide (0.37g, 5.69mmol) and heated to 65-70°C for 3hr. The mixture was cooled to room temperature and partitioned between diethyl ether and water. The organic phase was separated and the aqueous phase extracted again with diethyl ether. The combined organic solutions were then washed with brine, dried with
- 10 anhydrous magnesium sulfate and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent system of diethyl ether : pentane (1 : 1) to afford the title compound as a foam (2.2g). MS: 751 (MNa<sup>+</sup>).
- 15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 8.15 (1H, s), 7.20-7.36 (10H, m), 5.90 (1H, d), 5.70 (1H, br s), 4.58 (1H, t), 4.18-4.43 (4H, m), 4.90 (2H, s), 3.80 (1H, dd), 3.62 (1H, dd), 3.43 (3H, s), 0.90 (9H, s), 0.85 (9H, s), 0.01-0.09 (12H, m).

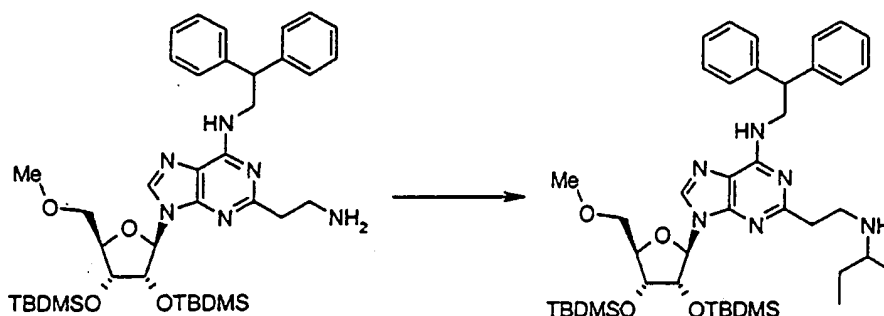
- PREPARATION 18:** *N*-{2-(2-Aminoethyl)-9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis[[*tert*-butyl(dimethyl)silyl]oxy]-5-(methoxymethyl)tetrahydro-2-furanyl]-9*H*-purin-6-yl}-*N*-(2,2-diphenylethyl)amine
- 20



A solution of 2-{9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}acetonitrile (1.9g, 2.6mmol) (preparation 17) in ethanol (40ml) saturated with ammonia gas was treated with Raney Nickel (400mg), pressurised to 414kPa (60psi) with hydrogen in a sealed vessel and stirred at room temperature for 4 days. The mixture was then filtered through Arbocel (trade mark) and the residue washed with ethanol. The solvent was removed under reduced pressure from the filtrate, the residue dissolved in pentane and the solvent again removed under reduced pressure to give the title compound as a powder (1.08g). MS: 733 (MH<sup>+</sup>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 8.11 (1H, s), 7.20-7.35 (10H, m), 5.94 (1H, d), 5.51 (1H, br s), 4.50 (1H, t), 4.30-4.42 (3H, m), 4.19 (1H, q), 3.79 (1H, dd), 3.60 (1H, dd), 3.41 (3H, s), 3.19 (2H, br s), 2.86 (2H, br t), 0.92 (9H, s), 0.87 (9H, s), 0.05 (12H, m).

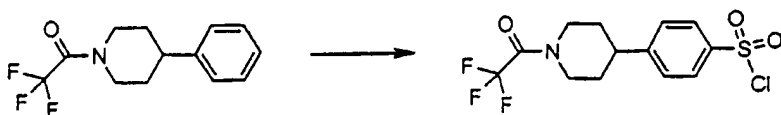
**PREPARATION 19 :** *N*-(2-{9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}ethyl)-*N*-(1-ethylpropyl)amine



Sodium triacetoxyborohydride (105mg, 0.51mmol) and glacial acetic acid (24mg, 0.40mmol) were added to a stirred solution of *N*-{2-(2-aminoethyl)-9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-9*H*-purin-6-yl}-*N*-(2,2-diphenylethyl)amine (250mg, 0.34mmol) (preparation 18) and diethyl ketone (58mg, 0.68mmol) in dichloromethane (15ml) and the resulting mixture stirred under an atmosphere of nitrogen gas at room temperature overnight. Additional portions of diethyl ketone (30mg, 0.35mmol) and sodium triacetoxyborohydride (60mg, 0.29mmol) were then added and stirring continued at room temperature for a further 24hr. The mixture was diluted with ethyl acetate (20ml) and washed sequentially with saturated aqueous sodium hydrogen carbonate solution, brine and water. The organic phase was separated and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with dichloromethane : methanol : ammonia (96 : 4 : 0.4) to give the title compound (250mg) as a gum. MS: 803 (MH<sup>+</sup>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ = 8.10 (1H, s), 7.19-7.35 (10H, m), 5.92 (1H, d), 5.49 (1H, br s), 4.16-4.50 (6H, m), 3.78 (1H, dd), 3.58 (1H, dd), 3.22 (3H, s), 2.97-3.11 (4H, m), 2.40 (1H, t), 1.38-1.48 (4H, m), 0.91 (9H, s), 0.86 (9H, s), 0.84 (6H, m), 0.04 (12H, t)

**PREPARATION 20: 4-[1-(2,2,2-Trifluoroacetyl)-4-piperidiny]benzenesulfonyl chloride**

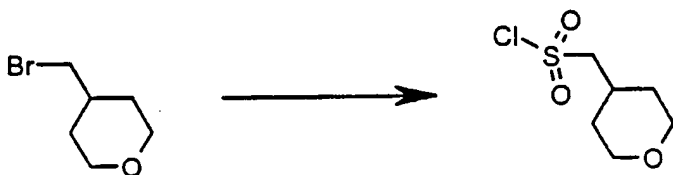


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Chlorosulfonic acid (56ml, 0.85 mol) was added dropwise to a stirred solution of 2,2,2-trifluoro-1-(4-phenyl-1-piperidiny)-1-ethanone (preparation 31) (34g, 0.13mol) in dichloromethane (500ml) at -15°C. The reaction mixture was then allowed to warm to room temperature and then stirred for 48hr. The resulting mixture was then poured into ice water and more dichloromethane (500 ml) was added. The organic phase was separated, dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure to give the title compound (41g) as a brown oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.00-7.95 (2H, m), 7.50-7.40 (2H, m), 4.80-4.65 (1H, m), 4.25-4.15 (1H, m), 3.40-3.20 (1H, m), 3.05-2.80 (2H, m), 2.10-1.95 (2H, m), 1.80-1.60 (2H, m).

**PREPARATION 21: Tetrahydro-2H-pyran-4-ylmethanesulfonyl chloride.**



20

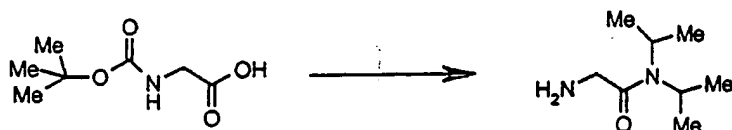
A stirred solution of 4-(bromomethyl)tetrahydro-2H-pyran (1.7g, 9.4mmol) (preparation 28) and sodium sulfite (4.78g, 18.0mmol) in a mixture of 1,4-dioxan (8ml) and water (8ml) was heated at reflux for 24hr. The reaction mixture was allowed to cool and then left to stand for 72hr. The solvent was removed under reduced pressure and the residue azeotroped with toluene three times. Thionyl chloride (17ml) and a couple of drops of N,N-dimethylformamide were added and the resulting mixture stirred and heated

25

under reflux for 1hr. The thionyl chloride was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was washed with water and brine then dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give the title compound (830mg) as an oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 4.00-3.90 (2H, m), 3.65-3.60 (2H, m), 3.50-3.40 (2H, m), 2.50-2.35 (1H, m), 1.90-1.80 (2H, m), 1.60-1.40 (2H, m).

10 **PREPARATION 22: 2-Amino-*N,N*-diisopropylacetamide.**

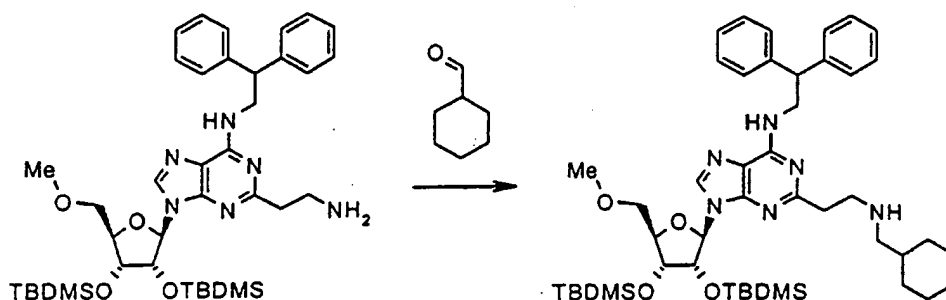


Trimethylacetylchloride (1.8g, 15mmol) was added to a stirred solution of 2-[[*tert*-butoxycarbonyl]amino]acetic acid (2.6g, 15mmol) and triethylamine (5ml, 36mmol) in dichloromethane (30ml) at 0°C. The reaction mixture was stirred for 10min and then *N*-ethyl-*N*-isopropyl-2-propanamine (2.5ml, 18mmol) was added. The reaction was allowed to warm to room temperature and stirred for 24hr. The solvent was removed under reduced pressure and the residue taken up into a mixture of methanol (30ml) and water (5ml). Concentrated hydrochloric acid (10ml) was added and the solution stirred for a further 3hr.

The reaction solvent was reduced to a low volume under reduced pressure, water (20ml) was added and the solution adjusted to a basic pH (>7) by addition of solid potassium carbonate. The aqueous phase was extracted with dichloromethane (x4). The dichloromethane extracts were combined, dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure to give the title compound (0.72g) as an oil. MS:  $\text{MH}^+$  159.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 3.90-3.70 (1H, m), 3.60-3.40 (1H, m), 3.35 (2H, s), 1.50-1.30 (6H, m), 1.30-1.10 (6H, m).

**PREPARATION 23:** *N*-(9-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-2-{2-[(cyclohexylmethyl)amino]ethyl}-9*H*-purin-6-yl)-*N*-(2,2-diphenylethyl)amine

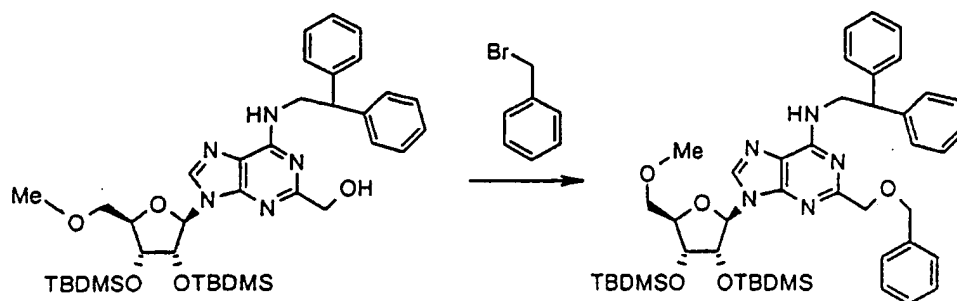


- 5 *N*-(2-(2-Aminoethyl)-9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-9*H*-purin-6-yl)-*N*-(2,2-diphenylethyl)amine (275mg, 0.38mmol) (preparation 18) and cyclohexanecarbaldehyde (42mg, 0.38mmol) were stirred together in dichloromethane (10ml) for 2min prior to the addition of sodium triacetoxyborohydride (120mg, 0.57mmol). The reaction
- 10 mixture was stirred for 24hr at room temperature and then ethyl acetate (70ml) added. The solution was washed with saturated aqueous hydrogen carbonate, water and brine, then the solvent removed under reduced pressure to give a residue which was purified by column chromatography on silica gel eluting with dichloromethane : methanol : ammonia (97 : 3 : 0.3). This gave the title
- 15 compound (215mg) as a gum. MS: 829 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.10 (1H, s), 7.35-7.15 (10H, m), 5.95-5.90 (1H, m), 5.50 (1H, br s), 4.50-4.45 (1H, m), 4.40-4.25 (4H, m), 4.20-4.15 (1H, m), 3.80-3.75 (1H, m), 3.60-3.55 (1H, m), 3.45 (3H, s), 3.10-3.00 (4H, m), 2.50-2.45 (2H, m),

20 1.75-1.40 (7H, m), 1.25-1.05 (4H, m), 0.95-0.85 (18H, m), 0.10-0.00 (12H, m).

**PREPARATION 24:** 2-[(Benzyloxy)methyl]-9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-*N*-(2,2-diphenylethyl)-9*H*-purin-6-amine

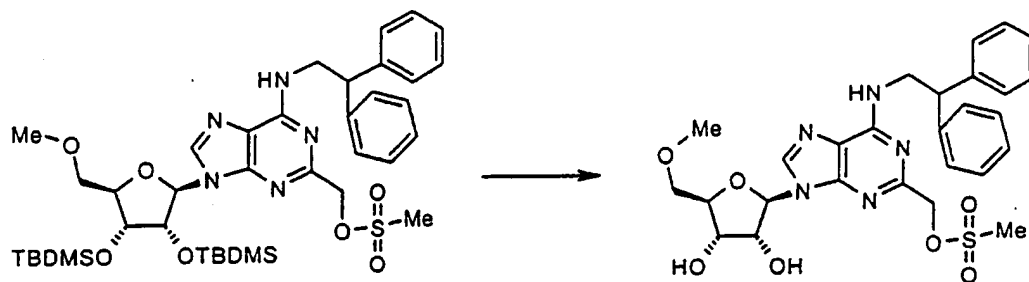


Sodium hydride (23mg of an 80% dispersion in mineral oil, 0.76mmol) was added to a stirred solution of {9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis[[*tert*-butyl(dimethyl)silyl]oxy]-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methanol (550mg, 0.76mmol) (preparation 15) in tetrahydrofuran (3ml). The reaction mixture was stirred at room temperature for 10min and then benzyl bromide (0.117ml, 1mmol) added. The reaction mixture was stirred for a further 24hr and then the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of hexane : ethyl acetate (3 : 1) rising in polarity to (2 : 1) to give the title compound (65mg) as a gum. MS: 832 (MNa<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.15 (1H, br s), 7.45-7.40 (2H, m), 7.30-7.15 (13H, m), 6.00-5.95 (1H, m), 5.70 (1H, br s), 4.75-4.60 (4H, m), 4.50-4.45 (1H, m), 4.40-4.30 (4H, m), 4.20-4.15 (1H, m), 3.80-3.75 (1H, m), 3.60-3.55 (1H, m), 3.40 (3H, s), 0.95-0.80 (18H, m), 0.50-0.00 (12H, m).

**PREPARATION 25:** {9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl methanesulfonate.

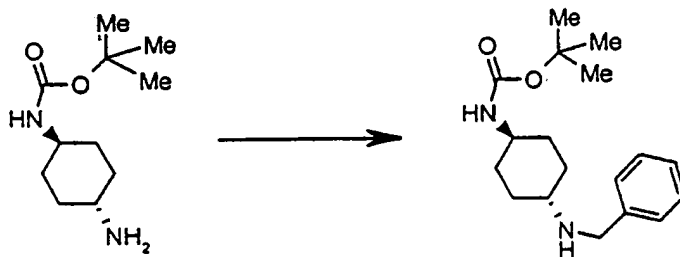




{9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis[[*tert*-butyl(dimethyl)silyl]oxy]-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl methanesulfonate (240mg, 0.3mmol) (preparation 16) was dissolved in stirred tetrahydrofuran (1ml) and a 1 molar solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (0.6ml, 0.6mmol) added. The reaction mixture was stirred at room temperature for 24hr. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol (95 : 5) increasing in polarity to dichloromethane : methanol (90 : 10). This gave the title compound (140mg) as a foam. MS: 570 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.95 (1H, s), 7.40-7.20 (10H, m), 5.95-5.80 (2H, m), 5.70 (1H, m), 5.30 (2H, m), 4.55-4.20 (6H, m), 3.65-3.50 (2H, m), 3.30 (3H, s), 3.10 (3H, s), 3.05 (1H, s).

#### PREPARATION 26: *tert*-Butyl trans-4-(benzylamino)cyclohexylcarbamate

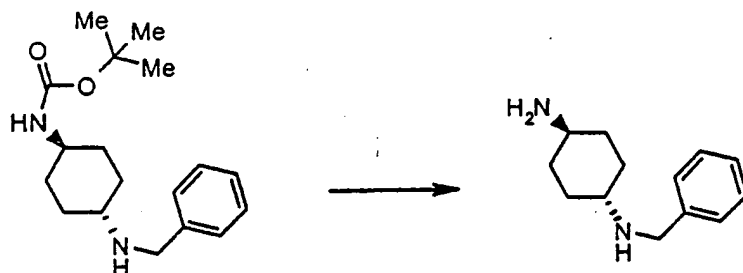


The title compound was prepared by a similar method to example 5 from *tert*-butyl trans-4-aminocyclohexylcarbamate (1.0g, 4.7mmol) (J. Org. Chem. 8811, 61, 1996), benzaldehyde (530mg, 5mmol) and sodium triacetoxyborohydride

(2.0g, 9.4mmol). The product was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (95 : 5 : 0.5) to give the title compound (0.73g) as a solid.

- 5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 7.35-7.20 (5H, m), 4.35 (1H, br s), 3.80 (2H, s), 3.40 (1H, br s), 2.50-2.40 (1H, m), 2.05-1.90 (4H, m), 1.45 (9H, s), 1.30-1.05 (4H, m).

**PREPARATION 27: *N*-(trans-4-Aminocyclohexyl)benzylamine**



- 10 A stirred solution of *tert*-butyl trans-4-(benzylamino)cyclohexylcarbamate (730mg, 3.6mmol) (preparation 26) in dichloromethane (20ml) was saturated with hydrogen chloride gas. The reaction mixture was stirred at room temperature for 2hr and the solvent removed under reduced pressure to give a residue which was triturated with diethyl ether. The resulting solid was
- 15 dissolved in water and solid sodium hydrogen carbonate added. The aqueous mixture was then extracted with ethyl acetate followed by dichloromethane. The organic extracts were combined, the solvent removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (95 : 5 : 0.5) to give
- 20 the title compound (530mg) as a gum.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 7.35-7.20 (5H, m), 3.80 (2H, s), 2.70-2.60 (1H, m), 2.50-2.40 (1H, m), 2.00-1.90 (2H, m), 1.90-1.80 (2H, m), 1.25-1.05 (4H, m).

- 25 **PREPARATION 28: 4-(Bromomethyl)tetrahydro-2H-pyran.**



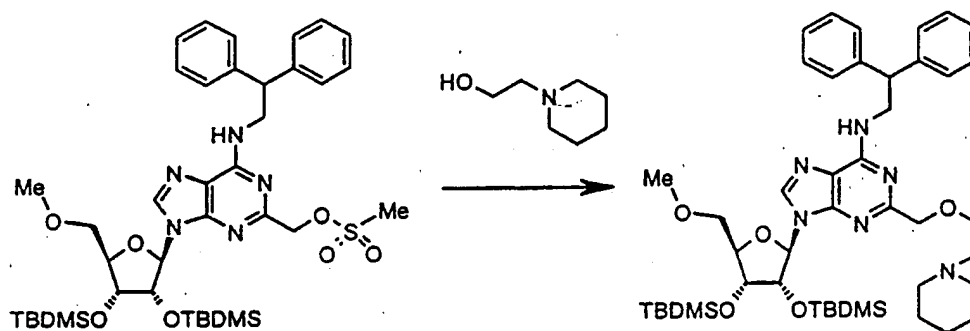
Triphenylphosphine (3.93g, 15mmol) was added to a stirred ice-cold solution of tetrahydro-2H-pyran-4-ylmethanol (1.16g, 10mmol) (WO 96/07410) and carbon tetrabromide (4.97g, 15mmol) in dichloromethane (50ml). The reaction

- 5 temperature was allowed to rise to room temperature and then the reaction mixture was stirred at room temperature for 24hr. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a gradient system of hexane rising in polarity to hexane : ethyl acetate (9 : 1) to give the title compound (1.7g) as an oil.

10

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 4.05-3.95 (2H, m), 3.45-3.25 (4H, m), 2.00-1.70 (3H, m), 1.40-1.20 (2H, m).

- 15 **PREPARATION 29:** *N*-(9-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-2-[(2-(1-piperidinyloxy)methyl)-9*H*-purin-6-yl]-*N*-(2,2-diphenylethyl)amine

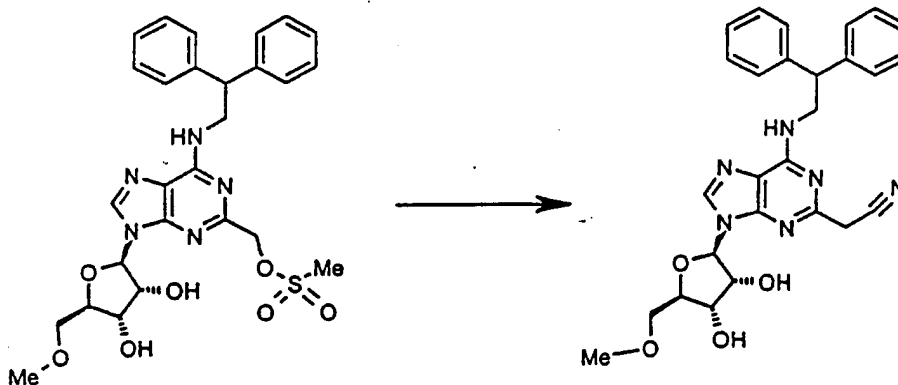


- 20 Sodium hydride (24mg of an 80% dispersion in mineral oil, 0.81mmol) was added to a stirred solution of {9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl methanesulfonate (500mg, 0.63mmol) (preparation 16) and 2-(1-piperidinyloxy)-1-ethanol (105mg, 0.81mmol) in tetrahydrofuran (5ml). The reaction mixture was stirred for 24hr at room

temperature and then heated at reflux for a further 8hr. The reaction mixture was then poured into cold water and extracted with ethyl acetate. The organic phase was separated, washed with brine and dried with anhydrous sodium sulfate. The solvent was then removed under reduced pressure to give a residue which was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol (95 : 5) to give the title compound (101mg) as an oil. MS: 833 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 8.15 (1H, s), 7.35-7.15 (10H, m), 6.00-5.95 (1H, m), 5.65 (1H, br s), 4.60 (2H, s), 4.50-4.45 (1H, m), 4.45-4.30 (4H, m), 4.20-4.15 (1H, m), 3.85-3.75 (3H, m), 3.60-3.55 (1H, m), 3.45 (3H, s), 2.75-2.40 (6H, m), 1.70-1.50 (4H, m), 1.50-1.35 (2H, m), 0.95-0.80 (18H, m), 0.10-0.00 (12H, m).

**PREPARATION 30: 2-{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}acetonitrile**



Potassium cyanide (22mg, 0.33mmol) was added to a stirred solution of {9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl methanesulfonate (130mg, 0.22mmol) (preparation 25) in *N,N*-dimethylformamide (3ml). The reaction mixture was heated to 70°C for 1.5hr, allowed to cool to room temperature and then partitioned between diethyl ether and water. The aqueous layer was washed with diethyl ether. The combined organic solutions were washed with brine and dried with anhydrous magnesium sulfate. The solvent was removed

under reduced pressure to give a residue that was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol (97 : 3). This gave the title compound (70mg) as a powder. MS: 523 (MNa<sup>+</sup>).

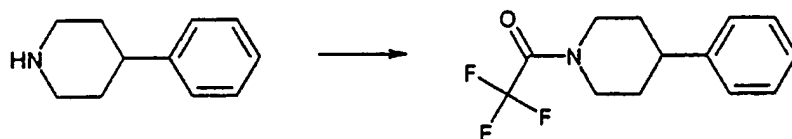
5

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.90 (1H, s), 7.40-7.20 (10H, m), 5.90-5.80 (2H, m), 5.40 (1H, s), 4.60-4.55 (1H, m), 4.50-4.20 (5H, m), 3.95 (2H, s), 3.65-3.50 (2H, m), 3.30 (3H, s), 3.05 (1H, s).

10 Analysis : Found C, 63.47, H, 5.71, N, 16.11; C<sub>27</sub>H<sub>28</sub>N<sub>6</sub>O<sub>4</sub> · 0.5H<sub>2</sub>O requires C, 63.64, H, 5.75, N, 16.49%.

**PREPARATION 31: 2,2,2-Trifluoro-1-(4-phenyl-1-piperidiny)-1-ethanone.**

15

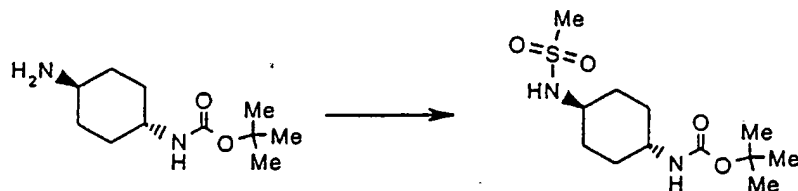


Trifluoroacetic anhydride (32.6g, 0.155mol) was slowly added to a stirred solution of 4-phenylpiperidine (25g, 0.155mol) and N-methylmorpholine (15.6g, 0.155mol) in dichloromethane (250ml) at between -10°C and -15°C. The reaction mixture was allowed to warm to room temperature and then stirred for a further 24hr. The reaction mixture was then washed with water (100ml), dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure to give a residue which was purified by column chromatography on silica gel eluting with hexane : ethyl acetate (7 : 3) to give the title compound (34.5g) as a gum.

25

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.40-7.15 (5H, m), 4.75-4.60 (1H, m), 4.25-4.10 (1H, m), 3.30-3.15 (1H, m), 2.90-2.70 (2H, m), 2.05-1.90 (2H, m), 1.80-1.60 (2H, m).

**PREPARATION 32: *tert*-Butyl trans-4-[(methylsulfonyl)amino]cyclohexylcarbamate.**

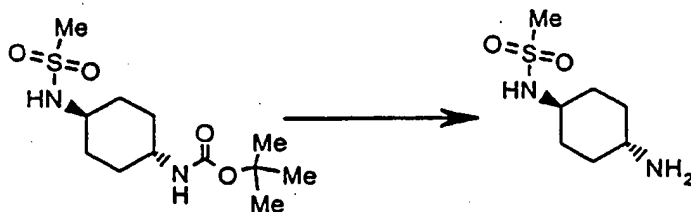


- 5 Methanesulfonyl chloride (0.56g, 4.7mmol) was added to a stirred solution of *tert*-butyl trans-4-aminocyclohexylcarbamate (J. Org. Chem. 8811, 61, 1996) (1.0g, 4.7mmol) and *N*-ethyl-*N*-isopropyl-2-propanamine (0.67g, 0.52mmol) in dichloromethane (30 ml). The reaction mixture was stirred for 30min at room temperature and then partitioned between ethyl acetate (300ml) and water
- 10 (100ml). The organic layer was washed twice with 1 molar aqueous citric acid solution and then with a saturated aqueous solution of sodium hydrogen carbonate, dried with anhydrous sodium sulfate and the solvent removed under reduced pressure to give a residue that was triturated with diethyl ether to give the title compound (0.99g) as a white solid.

15

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 4.35 (1H, br s), 4.15-4.10 (1H, m), 3.40 (1H, br s), 3.30-3.20 (1H, m), 2.95 (3H, br s), 2.10-2.00 (4H, m), 1.40 (9H, s), 1.40-1.15 (4H, m).

20 **PREPARATION 33: *N*-(trans-4-Aminocyclohexyl)methanesulfonamide**



A stirred solution of *tert*-butyl trans-4-

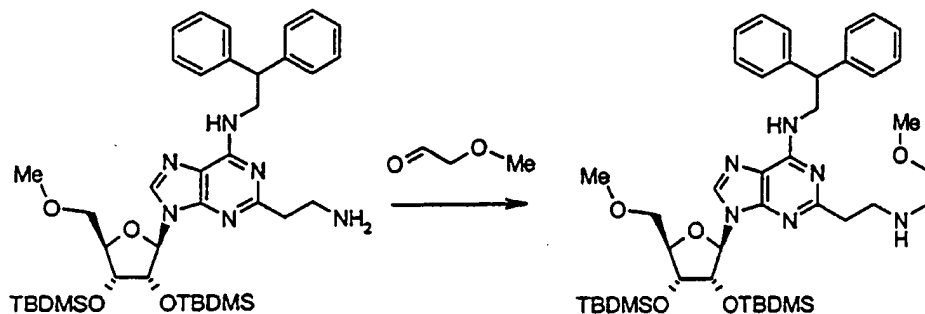
- 25 [(methylsulfonyl)amino]cyclohexylcarbamate (990mg, 3.39mmol) (preparation

32) in dichloromethane (25ml) at room temperature was saturated with hydrogen chloride gas. The reaction mixture was stirred at room temperature for 2hr and the solvent then removed under reduced pressure to give a colourless solid. The solid was triturated with diethyl ether and then suspended  
 5 in ethyl acetate and exposed to ultrasonic agitation for 5min. The remaining solid was filtered off to give the title compound (0.6g) as a solid.

<sup>1</sup>H NMR (d<sub>6</sub> DMSO) δ = 8.15-7.95 (3H, br s), 7.05-7.00 (1H, m), 3.10-3.00 (1H, m), 3.00 -2.80 (4H, m), 1.95-1.80 (4H, m), 1.45-1.15 (4H, m).

10

**PREPARATION 34:** *N*-(2-{9-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}ethyl)-*N*-(2-methoxyethyl)amine

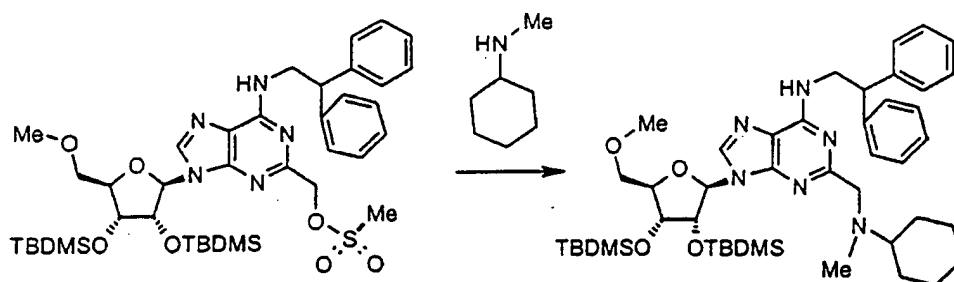


15 The title compound was prepared by a similar method to preparation 23 from the compound of preparation 18 (250mg, 0.34mmol), sodium triacetoxymethylborohydride (120mg, 0.56mmol) and 2-methoxyacetaldehyde (28mg, 0.33mmol). The compound was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (95 :  
 20 5 : 0.5) to give the title compound (155mg) as a foam. MS: 791 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.10 (1H, s), 7.35-7.20 (10H, m), 5.95 (1H, s), 5.50 (1H, br s), 4.50-4.45 (1H, m), 4.40-4.25 (4H, m), 4.20-4.15 (1H, m), 3.80-3.75 (1H, m), 3.60-3.55 (1H, m), 3.50-3.45 (2H, m), 3.40 (3H, s), 3.30 (3H, s), 3.15-2.95 (4H,  
 25 m), 2.90-2.80 (2H, m), 0.95-0.85 (18H, m), 0.10-0.00 (12H, m).

**PREPARATION 35:** *N*-(9-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-2-[(cyclohexyl(methyl)amino)methyl]-9*H*-purin-6-yl)-*N*-(2,2-diphenylethyl)amine.

5

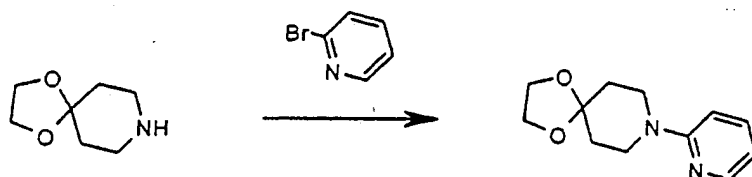


*N*-Cyclohexyl-*N*-methylamine (30mg, 0.27mmol) was added to a stirred solution of 9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl methanesulfonate (150mg, 0.19mmol) (preparation 16) and potassium carbonate (60mg, 0.44mmol) in acetonitrile (10ml). The reaction mixture was heated under reflux for 1hr and then partitioned between diethyl ether and water. The organic phase was removed and the aqueous phase extracted with more diethyl ether. The combined organic layers were washed with brine and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a residue which was purified by column chromatography on silica gel eluting with ethyl acetate. This gave the title compound (140mg) as a foam. MS: 815 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.15 (1H, s), 7.35-7.20 (10H, m), 6.00-5.95 (1H, m), 5.55 (1H, br s), 4.55-4.50 (1H, m), 4.45-4.30 (4H, m), 4.25-4.15 (1H, m), 3.85-3.70 (3H, m), 3.60-3.55 (1H, m), 3.45 (3H, s), 2.65-2.40 (4H, m), 2.05-1.95 (2H, m), 1.80-1.75 (2H, m), 1.35-1.00 (6H, m), 0.95-0.85 (18H, m), 0.10-0.00 (12H, m)

**PREPARATION 36:** 8-(2-Pyridinyl)-1,4-dioxo-8-azaspiro[4.5]decan

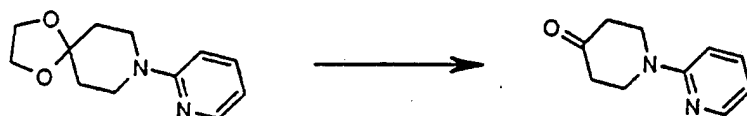




Potassium carbonate (700mg, 5mmol), 1,4-dioxaspiro[4.5]decane (1.43g, 10mmol) and 2-bromopyridine (1.58g, 10mmol) were stirred and heated together in N,N-dimethylformamide (10ml) at 125°C for 4hr. The reaction mixture was then poured into water and extracted with ethyl acetate. The organic phase was separated, washed with water and dried over solid potassium carbonate and the solvent removed under reduced pressure to give the title compound (1.1g) as an oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.20-8.10 (1H, m), 7.45-7.40 (1H, m), 6.70-6.60 (1H, m), 6.60-6.50 (1H, m), 3.95 (4H, s), 3.70-3.60 (4H, m), 1.80-1.70 (4H, m).

#### PREPARATION 37: 1-(2-Pyridinyl)-4-piperidinone

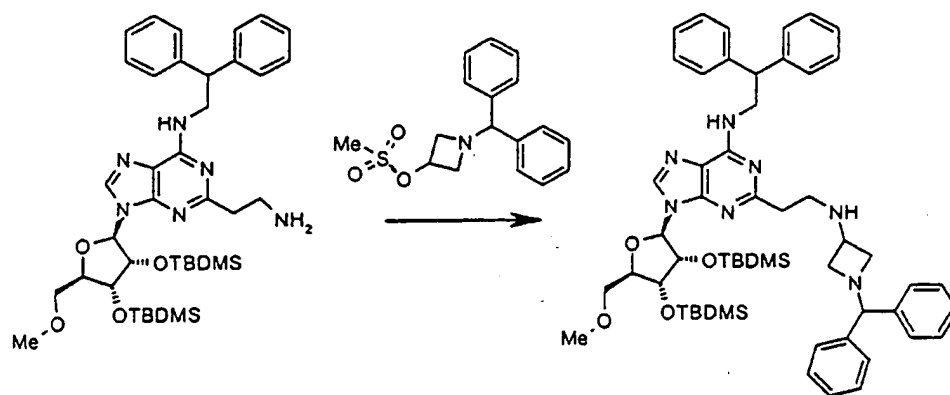


A solution of 8-(2-pyridinyl)-1,4-dioxaspiro[4.5]decane (23g, 0.1 mol) (preparation 36) in 10% w/v sulphuric acid was stirred at room temperature for 8hr. The reaction mixture was cooled in ice and then the solution adjusted to pH>7 with 0.88 ammonia. The solution was extracted with diethyl ether and the solvent removed from the organic extracts under reduced pressure to give the title compound (14.7g) as an oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.25-8.20 (1H, m), 7.60-7.50 (1H, m), 6.80-6.75 (1H, m), 6.75-6.65 (1H, m), 4.00-3.90 (4H, m), 2.60-2.45 (4H, m).

**PREPARATION 38: 2-{2-[(1-Benzhydryl-3-azetidiny]amino] thyl}-9-[(2R,3R,4R,5R)-3,4-bis[[(tert-butyl(dimethyl)silyl]oxy]-5-**

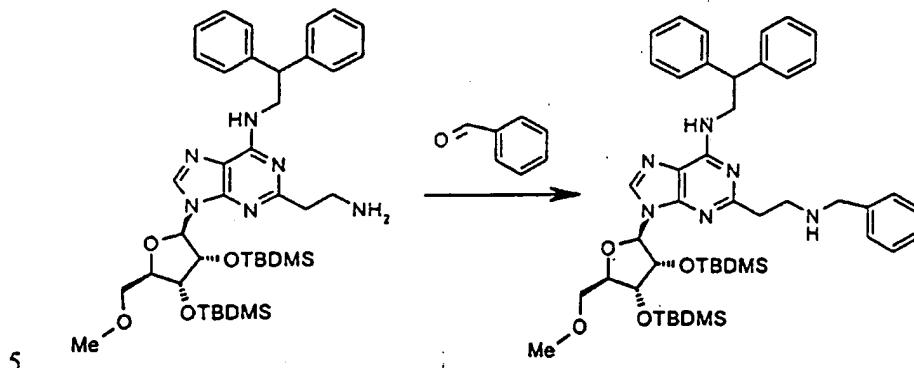
(methoxymethyl)tetrahydro-2-furanyl]-*N*-(2,2-diphenylethyl)-9*H*-purin-6-amine



- 5 1-Benzhydryl-3-azetidinyll methanesulfonate (90mg, 0.28mmol) and potassium carbonate (50mg, 0.36mmol) were added to a stirred solution of *N*-(2-(2-aminoethyl)-9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-9*H*-purin-6-yl)-*N*-(2,2-diphenylethyl)amine (200mg) (preparation 18) in acetonitrile (3ml). The reaction mixture was heated
- 10 at reflux for 5hr and then allowed to stand at room temperature for a further 24hr. The resulting mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was separated and the aqueous layer extracted with more ethyl acetate. The combined organic solutions were washed with brine and dried with anhydrous magnesium sulfate. The solvent was removed under
- 15 reduced pressure and the residue purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (98 : 2 : 0.2) to give the title compound (135mg) as a foam. MS: 955 (MH<sup>+</sup>).

- <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.10 (1H, s), 7.40-7.35 (4H, m), 7.30-7.10 (16H, m), 5.95-5.90 (1H, m), 5.50 (1H, br s), 4.50-4.45 (1H, m), 4.40-4.20 (5H, m), 4.20-4.15 (1H, m), 3.80-3.75 (1H, m), 3.60-3.45 (4H, m), 3.40 (3H, s), 3.05-2.90 (4H, m), 2.70-2.65 (2H, m), 0.90-0.85 (18H, m), 0.05-0.00 (12H, m).
- 20

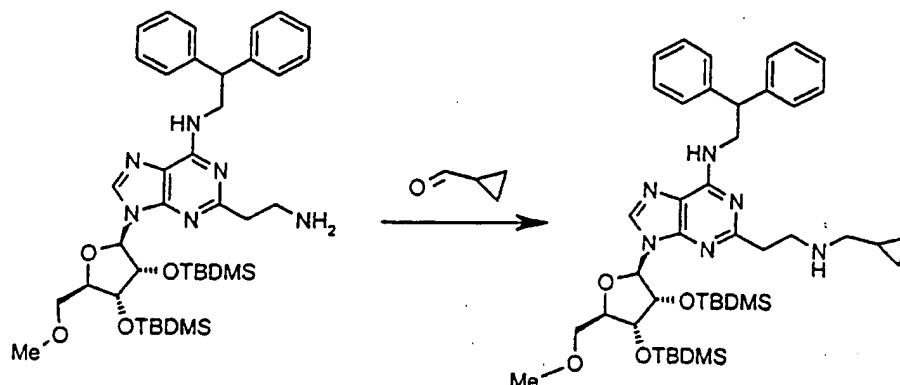
**PREPARATION 39:** *N*-Benzyl-*N*-(2-{9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]ethyl)amine.



The title compound was prepared by a similar method to example 5 from *N*-(2-(2-aminoethyl)-9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-9*H*-purin-6-yl)-*N*-(2,2-diphenylethyl)amine (430mg, 0.58mmol) (preparation 18), benzaldehyde (65mg, 0.61mmol) and sodium triacetoxyborohydride (270mg, 1.27mmol) in tetrahydrofuran (15ml). The product was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane rising in polarity to dichloromethane : methanol : ammonia (95 : 5 : 0.5) to give the title compound (360mg) as a foam. MS: 825 (MH<sup>+</sup>).

15  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.10 (1H, s), 7.40-7.15 (15H, m), 5.95-5.90 (1H, m), 5.60 (1H, br s), 4.50-4.45 (1H, m), 4.40-4.15 (5H, m), 3.85 (2H, s), 3.80-3.75 (1H, m), 3.60-3.55 (1H, m), 3.40 (3H, s), 3.20-3.00 (4H, m), 0.95-0.85 (18H, m), 0.10-0.00 (12H, m).

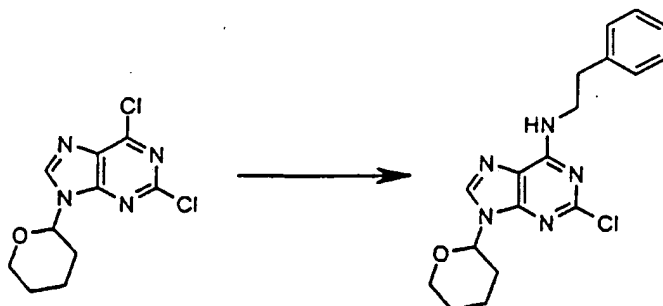
20  
**PREPARATION 40:** *N*-(9-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-2-{2-[(cyclopropylmethyl)amino]ethyl}-9*H*-purin-6-yl)-*N*-(2,2-diphenyl thyl)amin



The title compound was prepared by a similar method to example 5 from *N*-(2-(2-aminoethyl)-9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-9*H*-purin-6-yl)-*N*-(2,2-diphenylethyl)amine (430mg, 0.58mmol) (preparation 18), cyclopropanecarbaldehyde (45mg, 0.64mmol) and sodium triacetoxyborohydride (270mg, 1.27mmol) in tetrahydrofuran (10ml). The product was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane rising in polarity to dichloromethane : methanol : ammonia (95 : 5 : 0.5) to give the title compound (360mg) as a gum. MS: 788 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.10 (1H, s), 7.35-7.20 (10H, m), 5.95-5.90 (1H, m), 5.55 (1H, br s), 4.50-4.45 (1H, m), 4.40-4.25 (4H, m), 4.20-4.15 (1H, m), 3.80-3.75 (1H, m), 3.60-3.55 (1H, m), 3.40 (3H, s), 3.20-2.90 (4H, m), 2.50-2.45 (2H, m), 0.95-0.85 (19H, m), 0.45-0.40 (2H, m), 0.10-0.05 (14H, m).

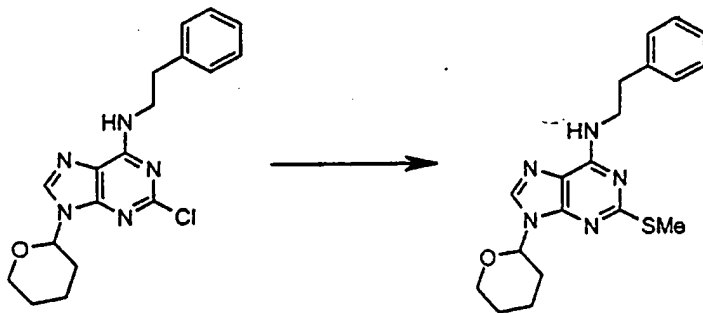
**PREPARATION 41: 2-Chloro-*N*-phenethyl-9-tetrahydro-2*H*-pyran-2-yl-9*H*-purin-6-amine.**



Phenethylamine (7.0g, 58.4mmol) was added to a stirred solution of 2,6-dichloro-9-tetrahydro-2H-pyran-2-yl-9H-purine (14.5g, 53.1mmol) (preparation 5) and triethylamine (21g, 212.5mmol) in acetonitrile (200ml). The reaction mixture was stirred for 3hr at room temperature and then more phenethylamine (1g, 8.3mmol) was added. The reaction mixture was stirred for a further 1hr and then the solvent was removed under reduced pressure to give a residue which was partitioned between diethyl ether (500ml) and water (250ml). The diethyl ether layer was washed with more water (300ml). The solvent was removed from the organic phase under reduced pressure to give a residue which was purified by column chromatography on silica gel eluting with diethyl ether to give the title compound (17.9g) as a white solid.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 7.90 (1H, br s), 7.35-7.20 (5H, m), 5.90 (1H, br s), 5.70-5.65 (1H, d), 4.20-4.10 (1H, m), 3.90 (1H, br s), 3.80-3.70 (1H, m), 3.00-2.95 (2H, m), 2.10-2.00 (2H, m), 2.00-1.85 (1H, m), 1.85-1.60 (3H, m).

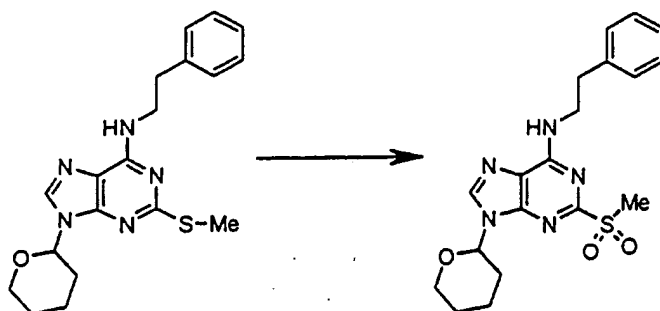
**PREPARATION 42: 2-(Methylsulfanyl)-N-phenethyl-9-tetrahydro-2H-pyran-2-yl-9H-purin-6-amine**



The title compound was prepared by a similar method to preparation 7 from 2-chloro-N-phenethyl-9-tetrahydro-2H-pyran-2-yl-9H-purin-6-amine (17.5g, 49mmol) (preparation 41) and sodium thiomethoxide (7.2g, 75mmol). This gave the title compound (16.7g) as a white solid.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 7.80 (1H, s), 7.35-7.20 (5H, m), 5.80-5.60 (2H, m), 4.20-4.10 (1H, m), 3.90 (2H, br s), 3.80-3.70 (1H, m), 3.00-2.90 (2H, m), 2.60 (3H, s), 2.15-1.90 (3H, m), 1.85-1.60 (3H, m).

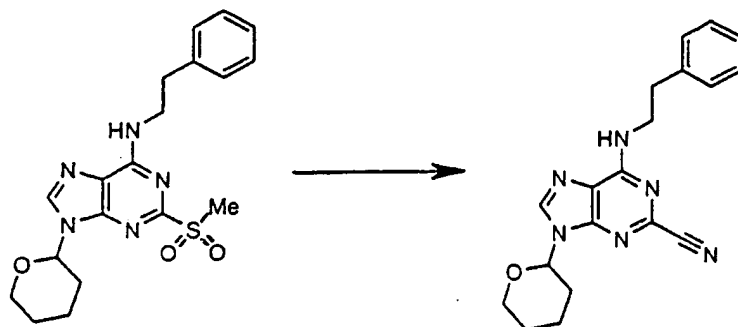
5 **PREPARATION 43: 2-(Methylsulfonyl)-*N*-phenethyl-9-tetrahydro-2*H*-pyran-2-yl-9*H*-purin-6-amine**



The title compound was prepared by a similar method to preparation 8 from 2-(methylsulfanyl)-*N*-phenethyl-9-tetrahydro-2*H*-pyran-2-yl-9*H*-purin-6-amine (16.7g, 45mmol) (preparation 42), Oxone (trade mark) (42.0g, 136mmol) and solid sodium hydrogen carbonate (20g, 238mmol). This gave the title compound (21.4g) as a white solid. MS: 402 ( $\text{MH}^+$ )

15  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 8.10 (1H, s), 7.35-7.20 (5H, m), 6.20 (1H, br s), 5.80-5.75 (1H, m), 4.20-4.10 (1H, m), 3.95 (1H, br s), 3.80-3.70 (1H, m), 3.30 (3H, s), 3.05-2.95 (2H, m), 2.20-1.60 (6H, m).

20 **PREPARATION 44: 6-(Phenethylamino)-9-tetrahydro-2*H*-pyran-2-yl-9*H*-purine-2-carbonitrile**



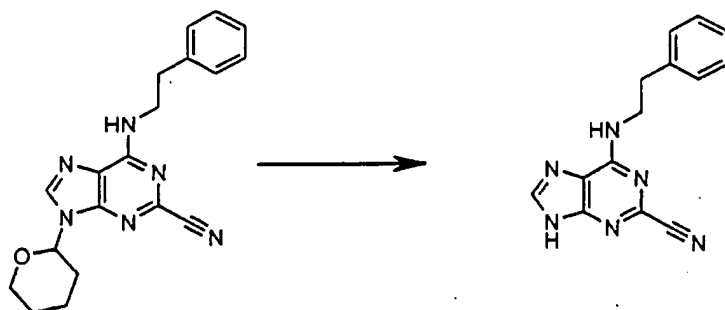
Potassium cyanide (5.6g, 86.2mmol) was added to a stirred solution of 2-(methylsulfonyl)-N-phenethyl-9-tetrahydro-2H-pyran-2-yl-9H-purin-6-amine (21.0g, 43.1mmol) (preparation 43) in N,N-dimethylformamide (100ml). The reaction mixture was heated at 110°C for 74hr with extra potassium cyanide being added at 44hr (3.3g, 50.8mmol) and 68hr (1.2g, 18.5mmol). The reaction mixture was allowed to stand at room temperature for 70hr, then poured into water (500ml), extracted with diethyl ether (1000ml) and the aqueous layer washed with diethyl ether (500ml). The combined organic layers were washed with water (3 x 500ml). The solvent was removed under reduced pressure from the combined organic layers to give a residue which was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol (99 : 1) to give the title compound (10.2g) as a brown solid. MS: 349 (MH<sup>+</sup>).

15

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.05 (1H, s), 7.35-7.20 (5H, m), 6.05 (1H, br s), 5.75-5.65 (1H, m), 4.20-4.10 (1H, m), 3.90 (1H, br s), 3.80-3.70 (1H, m), 3.05-2.90 (2H, m), 2.20-1.60 (6H, m).

20

**PREPARATION 45: 6-(Phenethylamino)-9H-purine-2-carbonitrile**

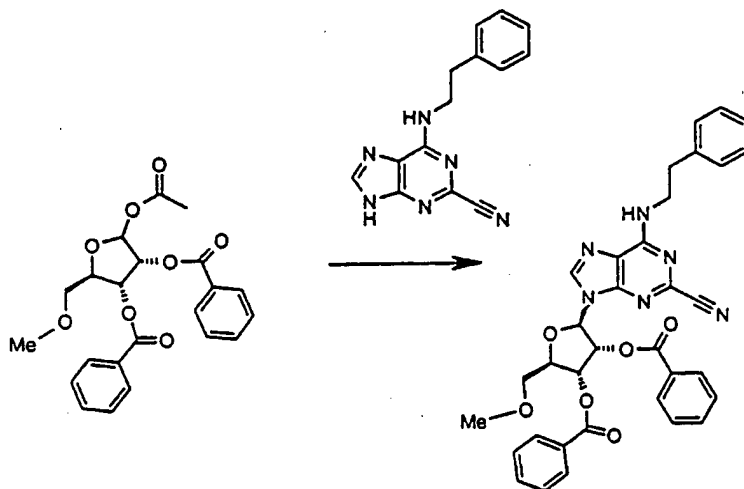


2 Molar hydrochloric acid (10ml) was added to a stirred solution of 6-(phenethylamino)-9-tetrahydro-2H-pyran-2-yl-9H-purine-2-carbonitrile (10.2g, 27.6mmol) (preparation 44) in ethanol (250ml) at 60°C. The solution was  
 5 allowed to cool to room temperature and the white solid that had been formed filtered off. After drying, this gave the title compound (6.1 g) as a white crystalline solid. MS: 265 (MH<sup>+</sup>)

<sup>1</sup>H NMR (d<sub>6</sub> DMSO)  $\delta$  = 8.40-8.20 (2H, m), 7.35-7.10 (5H, m), 3.75-3.60 (2H, m), 2.95-2.85 (2H, m).  
 10

**PREPARATION 46: (2R,3R,4R,5R)-4-(Benzoyloxy)-5-[2-cyano-6-(phenethylamino)-9H-purin-9-yl]-2-(methoxymethyl)tetrahydro-3-furanyl benzoate**

15

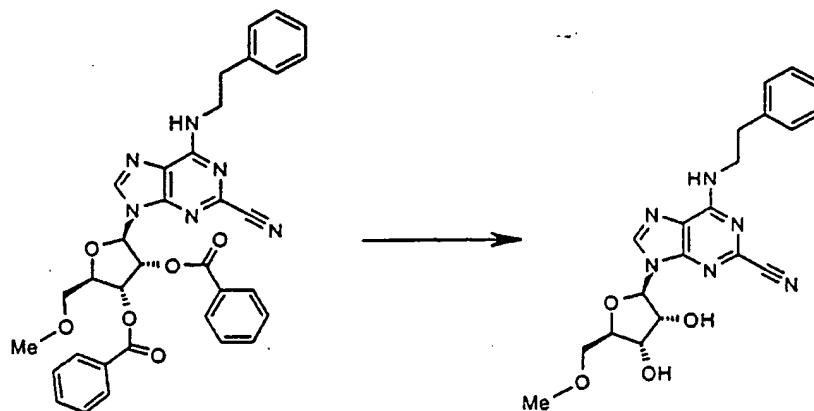




The title compound was prepared by a similar method to preparation 11 using 6-(phenethylamino)-9*H*-purine-2-carbonitrile (3.8g, 11.2mmol) (preparation 45), (2*R*,3*R*,4*R*,5*S*)-5-(acetyloxy)-4-(benzoyloxy)-2-(methoxymethyl)tetrahydro-3-furanyl benzoate and (2*R*,3*R*,4*R*,5*R*)-5-(acetyloxy)-4-(benzoyloxy)-2-(methoxymethyl)tetrahydro-3-furanyl benzoate (preparation 4) (6g, 14.5mmol), ammonium sulfate (200mg, 1.2mmol), 1,1,1,3,3,3-hexamethyldisilazane (150ml), bromotrimethylsilane (8ml, 177mmol), acetonitrile (80ml), dichloromethane (80ml) and bismuth tribromide (0.35g, 0.24mmol). The product was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol (99.5 : 0.5). This gave the title compound (7.9g) as a white foam. MS: 619 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.35 (1H, s), 8.05-8.00 (2H, m), 7.95-7.90 (2H, m), 7.65-7.20 (11H, m), 6.65-6.60 (1H, m), 6.05-5.90 (3H, m), 4.60 (1H, s), 3.95-3.80 (4H, m), 3.55 (3H, s), 3.00-2.90 (2H, m).

**PREPARATION 47: 9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-(phenethylamino)-9*H*-purine-2-carbonitrile**



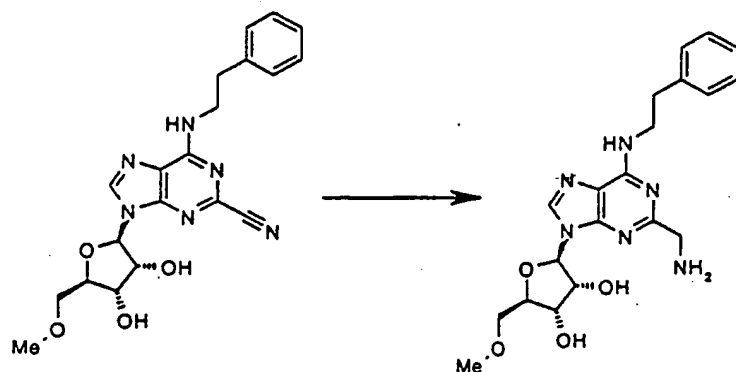
(2*R*,3*R*,4*R*,5*R*)-4-(Benzoyloxy)-5-[2-cyano-6-(phenethylamino)-9*H*-purin-9-yl]-2-(methoxymethyl)tetrahydro-3-furanyl benzoate (8.0g, 19.5mmol) (preparation

46) was dissolved in a saturated ethanolic solution of ammonia (300ml). The solution was allowed to stand at room temperature for 24hr, then re-saturated with ammonia gas and allowed to stand for a further 48hr. The solvent was then removed under reduced pressure and dichloromethane added to the residue.

5 The dichloromethane was then removed under reduced pressure and more dichloromethane (50ml) added. The insoluble material was filtered off and dried. This was found to be the title compound (3.1g) which was a solid.

$^1\text{H}$  NMR ( $d_6$  DMSO)  $\delta$  = 8.60-8.45 (2H, m), 7.30-7.15 (5H, m), 5.90-5.85 (1H, m), 5.55-5.50 (1H, m), 5.30-5.25 (1H, m), 4.55-4.50 (1H, m), 4.15-4.00 (2H, m), 3.70-3.65 (1H, m), 3.65-3.50 (2H, m), 3.30 (3H+HOD in DMSO, s), 2.95-2.90 (2H, m).

15 **PREPARATION 48: (2R,3R,4S,5R)-2-[2-(Aminomethyl)-6-(phenethylamino)-9H-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol**



A solution of 9-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-(phenethylamino)-9H-purine-2-carbonitrile (2.9g, 7.07mmol)  
20 (preparation 47) in ethanol (300ml), saturated with ammonia gas, was treated with 5% palladium on charcoal (1.0g), pressurised to 1034kPa (150psi) with hydrogen gas in a sealed vessel and stirred at room temperature for 48hr. The reaction mixture was filtered through Arbocel (trade mark) and the solvent  
25 removed under reduced pressure. The residue was dissolved in

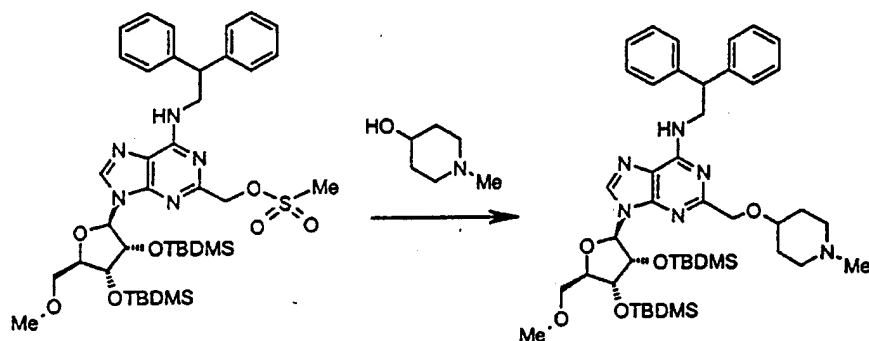
dichloromethane and the solvent removed under reduced pressure to give a product that was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane : methanol : ammonia (92 : 8 : 0.4) to give the title compound (1.7g) as a foam. MS: 416 (MH<sup>+</sup>)

5

<sup>1</sup>H NMR (d<sub>6</sub> DMSO) δ = 8.20 (1H, br s), 7.70 (1H, br s), 7.30-7.15 (5H, m), 5.90-5.85 (1H, m), 5.45 (1H, br s), 5.25 (1H, s), 4.60 (1H, s), 4.15-4.10 (1H, m), 4.00-3.95 (1H, m), 3.75-3.60 (3H, m), 3.60-3.45 (2H, m), 3.30-3.25 (3H+HOD in  
10 DMSO, s), 2.95-2.90 (2H, m)

**PREPARATION 49:** *N*-(9-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-2-[[1-methyl-4-piperidinyl]oxy]methyl]-9*H*-purin-6-yl)-*N*-(2,2-diphenylethyl)amine

15

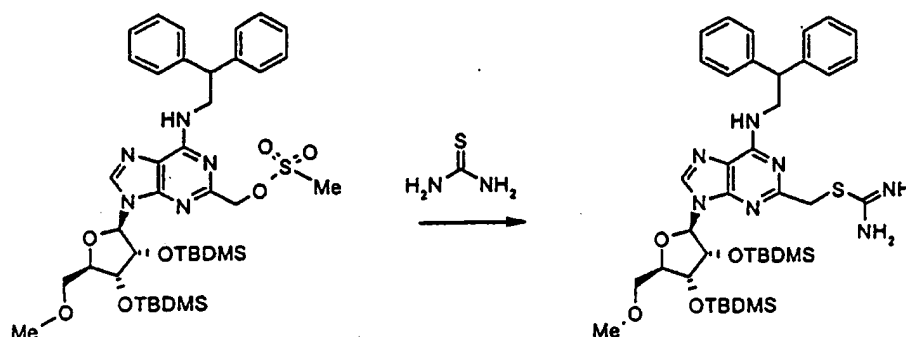


Sodium hydride (42mg of an 80% dispersion in mineral oil, 1.4mmol) was added to a stirred solution of 9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl)methyl methanesulfonate (preparation 16)  
20 (540 mg, 0.7mmol) and 1-methyl-4-piperidinol (160mg, 1.4mmol) in tetrahydrofuran (10ml). The reaction mixture was heated at reflux for 24hr and then the solvent removed under reduced pressure to give a residue which was

purified by column chromatography on silica gel eluting with dichloromethane : methanol (95 : 5) to give the title compound (68mg). MS: 818 (MH<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 8.20 (1H, s), 7.35-7.10 (10H, m), 6.00-5.95 (1H, m), 5.65 (1H, br s), 4.60 (2H, s), 4.50-4.10 (6H, m), 3.80-3.70 (1H, m), 3.70-3.50 (2H, m), 3.40 (3H, s), 3.40-3.30 (2H, m), 2.80-2.70 (2H, m), 2.30-2.20 (5H, m), 2.05-1.95 (2H, m), 0.95-0.80 (18H, m), 0.10-0.00 (12H, m).

PREPARATION 50: 2-({[Amino(imino)methyl]sulfanyl)methyl}-9-  
 10 [(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-  
 purine

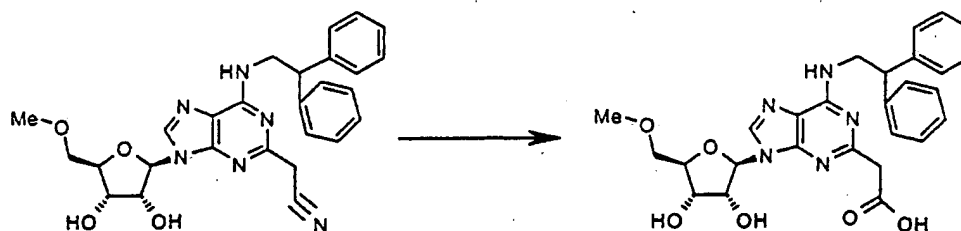


A stirred solution of thiourea (95mg, 1.25mmol) and {9-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl methanesulfonate (200mg,  
 15 0.25mmol) (preparation 16) in acetone (5ml) was heated at reflux for 24hr. The reaction mixture was then cooled and partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate. The ethyl acetate layer was  
 20 washed with brine and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give the title compound (0.18g) as a foam.

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 8.10 (1H, s), 7.30-7.20 (10H, m), 7.20-7.10 (2H, m), 5.85-  
 25 5.80 (2H, m), 4.40-4.35 (1H, m), 4.35-4.30 (1H, m), 4.25-4.20 (1H, m), 4.20-

4.00 (4H, m), 3.70-3.65 (1H, m), 3.55-3.50 (1H, m), 3.35 (3H, m), 0.85-0.75 (18H, m), 0.05 and -0.10 (12H, m).

5 **PREPARATION 51: 2-{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}acetic acid**



A stirred solution of 2-{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}acetonitrile (preparation 30) (1.5g, 3mmol) in methanol (30ml) and an aqueous 1 molar solution of sodium hydroxide (10ml) was heated at reflux for 24hr. The methanol was then removed under reduced pressure and the residual liquid diluted with more water and washed twice with ethyl acetate. The aqueous phase was acidified to pH <7 with a 1 molar aqueous citric acid solution and then extracted twice with ethyl acetate. The extracts were combined, washed with brine and dried with anhydrous magnesium sulfate. The residue, after removal of the solvent under reduced pressure, was dissolved into diethyl ether and the solvent removed again twice under reduced pressure to give the title compound (1.25g) as a foam. MS: 518 (M-H<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.00 (1H, s), 7.40-7.10 (10H, m), 6.20 (1H, br s), 5.95 (1H, s), 4.50-4.10 (6H, m), 3.90 (2H, m), 3.70-3.50 (2H, m), 3.30 (3H, s).

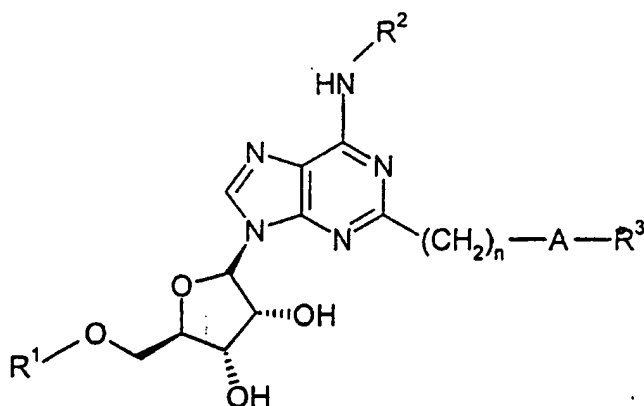
### PHARMACOLOGICAL ACTIVITY

All the compounds prepared in the Examples section were tested for their ability to inhibit neutrophil function by the method described on pages 21 and 22 and  
5 they all demonstrated submicromolar  $IC_{50}$  values in this assay.

CLAIMS

1. A compound of formula (I):

5



15 wherein

R¹ is alkyl or cyclopropylmethyl;

R² is phenyl-alkylene or naphthyl-alkylene, said alkylene chain being optionally further substituted by phenyl or naphthyl, each phenyl or naphthyl being  
 20 optionally substituted by one or more substituents each independently selected from alkyl, alkoxy, halo and cyano;

n is 1 or 2;

25 A is NR<sup>a</sup>, NR<sup>a</sup>C(O), NR<sup>a</sup>C(O)NR<sup>a</sup>, NR<sup>a</sup>C(O)O, OC(O)NR<sup>a</sup>, C(O)NR<sup>a</sup>, NR<sup>a</sup>SO<sub>2</sub>, SO<sub>2</sub>NR<sup>a</sup>, O, S or SO<sub>2</sub>;

R<sup>a</sup> is H, alkyl or benzyl optionally ring-substituted by one or more substituents each independently selected from alkyl, alkoxy, halo and cyano;

30

R³ is a group of the formula -(CH<sub>2</sub>)<sub>p</sub>-R<sup>p</sup>-B;

p is 0, 1 or 2;

$R^p$  is a bond, alkylene, cycloalkylene, phenylene or naphthylene, said cycloalkylene, phenylene and naphthylene each being optionally substituted by  
5 one or more substituents each independently selected from alkyl, alkoxy, halo and alkoxyalkylene;

B is

- (i) H,  $-NR^bR^b$ ,  $R^bR^bN$ -alkylene,  $-OR^b$ ,  $-COOR^b$ ,  $-OCOR^b$ ,  $-SO_2R^b$ ,  $-CN$ ,  $-SO_2NR^bR^b$ ,  $-NR^bCOR^b$ ,  $-NR^bSO_2R^b$  or  $-CONR^bR^b$ , in which each  $R^b$  is the  
10 same or different and is selected from H, alkyl, phenyl and benzyl, provided that,  
(a) when B is  $-OCOR^b$ ,  $-SO_2R^b$ ,  $-NR^bCOR^b$  or  $-NR^bSO_2R^b$ , then the terminal  $R^b$  is not H, and,  
15 (b)  $R^p$  is a bond, p is 0 and B is H only when A is  $NR^a$ ,  $NR^aC(O)NR^a$ ,  $OC(O)NR^a$ ,  $C(O)NR^a$ ,  $SO_2NR^a$ , O or S,  
(ii) an optionally-substituted, fully- or partially-saturated or -unsaturated, mono- or bicyclic, heterocyclic group, which is linked to  $R^p$  by a ring carbon atom, or  
20 (iii) N-linked azetidiny, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl, each optionally substituted by one or more alkyl substituents, with the proviso that  $-(CH_2)_p-R^p$  is not  $-CH_2-$ ; and

where A is  $NR^a$ ,  $C(O)NR^a$ ,  $OC(O)NR^a$  or  $SO_2NR^a$ ,  $R^a$  and  $R^3$  taken together with  
25 the nitrogen atom to which they are attached can form an azetidine, pyrrolidine, piperidine or piperazine ring, optionally substituted by one or more alkyl substituents:

or a pharmaceutically acceptable salt or solvate thereof.

30

2. A compound as claimed in claim 1 wherein



$R^1$  is  $C_1$ - $C_6$  alkyl or cyclopropylmethyl;

$R^2$  is phenyl- $(C_1$ - $C_6)$ -alkylene or naphthyl- $(C_1$ - $C_6)$ -alkylene, said  $C_1$ - $C_6$  alkylene chain being optionally further substituted by phenyl or naphthyl, each phenyl or  
 5 naphthyl being optionally substituted by one or more substituents each independently selected from  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halo and cyano;

$n$  is 1 or 2;

10  $A$  is  $NR^a$ ,  $NR^aC(O)$ ,  $NR^aC(O)NR^a$ ,  $NR^aC(O)O$ ,  $OC(O)NR^a$ ,  $C(O)NR^a$ ,  $NR^aSO_2$ ,  $SO_2NR^a$ ,  $O$ ,  $S$  or  $SO_2$ ;

$R^a$  is  $H$ ,  $C_1$ - $C_6$  alkyl or benzyl optionally ring-substituted by one or more substituents each independently selected from  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halo  
 15 and cyano;

$R^3$  is a group of the formula  $-(CH_2)_p-R^p-B$ ;

$p$  is 0, 1 or 2;

20

$R^p$  is a bond,  $C_1$ - $C_6$  alkylene,  $C_3$ - $C_7$  cycloalkylene, phenylene or naphthylene, said  $C_3$ - $C_7$  cycloalkylene, phenylene and naphthylene each being optionally substituted by one or more substituents each independently selected from  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halo and  $C_1$ - $C_6$  alkoxy- $C_1$ - $C_6$ -alkylene;

25

$B$  is

(i)  $H$ ,  $-NR^bR^b$ ,  $R^bR^bN$ -( $C_1$ - $C_6$ )-alkylene,  $-OR^b$ ,  $-COOR^b$ ,  $-OCOR^b$ ,  $-SO_2R^b$ ,  $-CN$ ,  $-SO_2NR^bR^b$ ,  $-NR^bCOR^b$ ,  $-NR^bSO_2R^b$  or  $-CONR^bR^b$ , in which each  $R^b$  is the same or different and is selected from  $H$ ,  $C_1$ - $C_6$  alkyl, phenyl and  
 30 benzyl, provided that,

(a) when  $B$  is  $-OCOR^b$ ,  $-SO_2R^b$ ,  $-NR^bCOR^b$  or  $-NR^bSO_2R^b$ , then the terminal  $R^b$  is not  $H$ , and,

- (b)  $R^p$  is a bond,  $p$  is 0 and  $B$  is H only when  $A$  is  $NR^a$ ,  $NR^aC(O)NR^a$ ,  $OC(O)NR^a$ ,  $C(O)NR^a$ ,  $SO_2NR^a$ , O or S,
- (ii) an optionally-substituted, fully- or partially-saturated or -unsaturated, mono- or bicyclic, heterocyclic group, which is linked to  $R^p$  by a ring carbon atom, or
- (i) N-linked azetidiny, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl, each optionally substituted by one or more  $C_1$ - $C_6$  alkyl substituents, with the proviso that  $-(CH_2)_p-R^p$  is not  $-CH_2-$ ; and
- 10 where  $A$  is  $NR^a$ ,  $C(O)NR^a$ ,  $OC(O)NR^a$  or  $SO_2NR^a$ ,  $R^a$  and  $R^3$  taken together with the nitrogen atom to which they are attached can form an azetidine, pyrrolidine, piperidine or piperazine ring, each optionally substituted by one or more  $C_1$ - $C_6$  alkyl substituents.
- 15 3. A compound as claimed in claim 1 or 2 wherein in the definition of  $B$ , said optionally-substituted, fully- or partially-saturated or -unsaturated, mono- or bicyclic, heterocyclic group, which is linked to  $R^p$  by a ring carbon atom, has from 4 to 12 ring atoms each independently selected from C, N, O and S.
- 20 4. A compound as claimed in claim 3 wherein in the definition of  $B$ , said optionally-substituted, fully- or partially-saturated or -unsaturated, mono- or bicyclic, heterocyclic group, which is linked to  $R^p$  by a ring carbon atom, has from 4 to 10 ring atoms each independently selected from C, N, O and S.
- 25 5. A compound as claimed in claim 3 or 4 wherein in the definition of  $B$ , said optionally-substituted, fully- or partially-saturated or -unsaturated, mono- or bicyclic, heterocyclic group, which is linked to  $R^p$  by a ring carbon atom, has ring atoms selected from 1 to 4 N atoms, 1 or 2 O and 1 or 2 S atoms, with the remaining ring atoms being C atoms.
- 30

6. A compound as claimed in claim 5 wherein in the definition of B, said optionally-substituted, fully- or partially-saturated or -unsaturated, mono- or bicyclic, heterocyclic group, which is linked to R<sup>p</sup> by a ring carbon atom, has from 1 to 4 ring N atoms, or 1 or 2 ring N atoms and 1 O or 1 S ring atom, or 1 O or 1 S ring atom, with the remaining ring atoms being C atoms.
7. A compound as claimed in any one of the preceding claims wherein said fully- or partially-saturated or -unsaturated, mono- or bicyclic, heterocyclic group, which is linked to R<sup>p</sup> by a ring carbon atom, is optionally substituted by one or more substituents each independently selected from R<sup>5</sup>, -OR<sup>5</sup>, halo, oxo, hydroxy, cyano, -COR<sup>5</sup>, -COOH, -COOR<sup>5</sup>, -CONH<sub>2</sub>, -CONHR<sup>5</sup>, -CONR<sup>5</sup>R<sup>5</sup>, amino, -NHR<sup>5</sup>, -NR<sup>5</sup>R<sup>5</sup>, -SO<sub>2</sub>R<sup>5</sup>, -SO<sub>2</sub>NH<sub>2</sub>, -SO<sub>2</sub>NHR<sup>5</sup>, -SO<sub>2</sub>NR<sup>5</sup>R<sup>5</sup>, -NHCOR<sup>5</sup>, -NR<sup>5</sup>COR<sup>5</sup>, -NHSO<sub>2</sub>R<sup>5</sup>, -NR<sup>5</sup>SO<sub>2</sub>R<sup>5</sup> and pyridinyl, wherein R<sup>5</sup> is C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, phenyl or naphthyl, each optionally substituted by C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>1</sub>-C<sub>8</sub> alkoxy, halo, phenyl, naphthyl or benzylamino.
8. A compound as claimed in any one of the preceding claims wherein R<sup>1</sup> is C<sub>1</sub>-C<sub>8</sub> alkyl.
9. A compound as claimed in claim 8 wherein R<sup>1</sup> is methyl.
10. A compound as claimed in any one of the preceding claims wherein R<sup>2</sup> is phenyl-(C<sub>1</sub>-C<sub>8</sub>)-alkylene, said C<sub>1</sub>-C<sub>8</sub> alkylene chain being optionally further substituted by phenyl.
11. A compound as claimed in claim 10 wherein R<sup>2</sup> is 2-phenylethyl, said ethyl chain being optionally further substituted by phenyl.
12. A compound as claimed in claim 11 wherein R<sup>2</sup> is 2-phenylethyl or 2,2-

diphenylethyl.

13. A compound as claimed in claim 12 wherein  $R^2$  is 2,2-diphenylethyl.
- 5 14. A compound as claimed in any one of the preceding claims wherein A is  $NR^a$ ,  $NR^aC(O)$ ,  $NR^aC(O)O$ ,  $C(O)NR^a$ ,  $NR^aSO_2$ ,  $SO_2NR^a$ , O, S or  $SO_2$ .
15. A compound as claimed in claim 14 wherein A is  $NR^a$  or  $NR^aSO_2$ .
- 10 16. A compound as claimed in any one of the preceding claims wherein  $R^a$  is H,  $C_1$ - $C_6$  alkyl or benzyl optionally ring-substituted by one or more  $C_1$ - $C_6$  alkoxy substituents.
- 15 17. A compound as claimed in claim 16 wherein  $R^a$  is H, methyl, 2-methylprop-1-yl or methoxybenzyl.
18. A compound as claimed in claim 17 wherein  $R^a$  is H, methyl, 2-methylprop-1-yl or 2-methoxybenzyl.
- 20 19. A compound as claimed in claim 1 or 2 wherein  $R^3$  is  
H,  
 $C_1$ - $C_6$  alkyl optionally substituted by  $C_3$ - $C_7$  cycloalkyl,  $C_1$ - $C_6$  alkoxy,  
amino,  $-NH(C_1$ - $C_6$  alkyl),  $-N(C_1$ - $C_6$  alkyl) $_2$ ,  $-CONH_2$ ,  $-CONH(C_1$ - $C_6$  alkyl),  $-$   
CON( $C_1$ - $C_6$  alkyl) $_2$ , phenyl (optionally substituted by halo,  $C_1$ - $C_6$  alkoxy,  
25  $C_1$ - $C_6$  alkoxy-( $C_1$ - $C_6$ )-alkylene, amino-( $C_1$ - $C_6$ )-alkylene, cyano or  
piperidinyl (optionally substituted by  $C_1$ - $C_6$  alkyl, halo-( $C_1$ - $C_6$ )-alkyl or  
halo-( $C_1$ - $C_6$ )-alkanoyl)), piperidinyl or tetrahydropyranyl,  
 $C_3$ - $C_7$  cycloalkyl optionally substituted by  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  
benzylamino or  $C_1$ - $C_6$  alkanesulphonamido,  
30 phenyl optionally substituted by halo,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkoxy-( $C_1$ - $C_6$ )-  
alkylene, amino-( $C_1$ - $C_6$ )-alkylene or piperidinyl (optionally substituted by  
 $C_1$ - $C_6$  alkyl, halo-( $C_1$ - $C_6$ )-alkyl or halo-( $C_1$ - $C_6$ )-alkanoyl), or

azetidiny, pyridiny, piperidiny, tetrahydrothiopyrany or 1,2,3,4-tetrahydroisoquinoliny, each optionally substituted by C<sub>1</sub>-C<sub>6</sub> alkyl, benzhydryl, halo-(C<sub>1</sub>-C<sub>6</sub>)-alkanoyl, oxo, hydroxy, cyano, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, benzoyl or pyridiny.

- 5
20. A compound as claimed in claim 19 wherein R<sup>3</sup> is H, methyl, n-propyl, i-propyl, 2-methylprop-1-yl, 2,2-dimethylprop-1-yl, n-butyl, t-butyl, pentan-3-yl, cyclopentyl, cyclohexyl, 4-(isopropyl)cyclohexyl, cyclopropylmethyl, cyclohexylmethyl, 2-methoxyethyl, 2-dimethylaminoethyl, 2-(N,N-
- 10 dimethylcarbamoyl)ethyl, N,N-(diisopropyl)carbamoylmethyl, 2-(N-t-butylcarbamoyl)ethyl, phenyl, benzyl, 4-chlorobenzyl, 2-methoxybenzyl, 3,4-dimethoxybenzyl, 4-(isopropoxy)benzyl, 2-methoxymethylbenzyl, 4-aminomethylbenzyl, 4-cyanobenzyl, 4,4-dimethylcyclohexyl, 4-methoxycyclohexyl, 4-benzylaminocyclohexyl, 4-
- 15 methanesulphonamidocyclohexyl, 2-piperidinoethyl, 4-(piperidin-4-yl)phenyl, 4-(1-trifluoroacetyl)piperidin-4-yl)phenyl, 1-benzhydrylazetid-3-yl, 2,6-dimethylpyridin-3-yl, 5-cyanopyridin-2-yl, 1-methylpiperidin-4-yl, 1-(isopropyl)piperidin-4-yl, 1-t-butoxycarbonylpiperidin-4-yl, 1-benzoylpiperidin-4-yl, 1-(2-pyridinyl)piperidin-4-yl, 1,1-
- 20 dioxotetrahydrothiopyran-4-yl, tetrahydropyran-4-ylmethyl, 5-methyl-1,2,3,4-tetrahydroisoquinolin-8-yl or 5-methyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-8-yl.
21. A compound as claimed in claim 20 wherein R<sup>3</sup> is phenyl, cyclohexyl, 5-
- 25 methyl-1,2,3,4-tetrahydroisoquinolin-8-yl, 2-methylprop-1-yl, i-propyl, 2-methoxybenzyl or N,N-(diisopropyl)carbamoylmethyl.
22. A compound as claimed in claim 1 or 2 wherein -A-R<sup>3</sup> is amino, isopropylamino, pentan-3-ylamino, 2-methylprop-1-ylamino, di(2-
- 30 methylprop-1-yl)amino, N-cyclohexyl-N-methylamino, 2-methoxyethylamino, 2-(N,N-dimethylcarbamoyl)ethylamino, N,N-(diisopropyl)carbamoylmethylamino, 2-(N-t-butylcarbamoyl)ethylamino,

- cyclopentylamino, cyclohexylamino, 4,4-dimethylcyclohexylamino, 4-(isopropyl)cyclohexylamino, 4-methoxycyclohexylamino, cis-4-methoxycyclohexylamino, trans-4-methoxycyclohexylamino, 4-benzylaminocyclohexylamino, trans-4-benzylaminocyclohexylamino, 4-methanesulphonamidocyclohexylamino, trans-4-methanesulphonamidocyclohexylamino, cyclopropylmethylamino, cyclohexylmethylamino, benzylamino, 4-chlorobenzylamino, 2-methoxybenzylamino, di(2-methoxybenzyl)amino, 4-(isopropoxy)benzylamino, 3,4-dimethoxybenzylamino, 2-methoxymethylbenzylamino, 4-aminomethylbenzylamino, 4-cyanobenzylamino, 1-benzhydrylazetidino-3-ylamino, 2,6-dimethylpyridin-3-ylamino, 5-cyanopyridin-2-ylamino, 1-methylpiperidin-4-ylamino, 1-(isopropyl)piperidin-4-ylamino, 1-(t-butoxycarbonyl)piperidin-4-ylamino, 1-benzoylpiperidin-4-ylamino, 1-(pyridin-2-yl)piperidin-4-ylamino, 2-piperidinoethylamino, 1,1-dioxotetrahydrothiopyran-4-ylamino, benzamido, phenylacetamido, t-butoxycarbonylamino, methanesulphonamido, n-propylsulphonylamido, i-propylsulphonylamido, n-butylsulphonamido, 2-methylprop-1-ylsulphonamido, 2,2-dimethylprop-1-ylsulphonamido, 2-methoxyethylsulphonamido, phenylsulphonylamido, benzylsulphonamido, 4-(piperidin-4-yl)phenylsulphonylamido, 4-(1-trifluoroacetylpiperidin-4-yl)phenylsulphonylamido, tetrahydropyran-4-ylmethylsulphonamido, 5-methyl-1,2,3,4-tetrahydroisoquinolin-8-ylsulphonylamido, 5-methyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-8-ylsulphonylamido, benzylaminosulphonyl, 2-(N,N-dimethylamino)ethoxy, benzyloxy, 2-piperidinoethoxy, 1-methylpiperidin-4-yloxy, phenylthio, benzylthio or benzylsulphonyl, or is 4-isopropylpiperidinocarbonyl.
23. A compound as claimed in claim 22 wherein -A-R<sup>3</sup> is phenylsulphonamido, cyclohexylamino, 5-methyl-1,2,3,4-tetrahydroisoquinolin-8-ylsulphonylamido, 2-methylprop-1-ylamino, i-propylamino, 2-methoxybenzylamino, N,N-

(diisopropyl)carbamoylmethylamino or 2-methylprop-1-ylsulphonamido.

24. A pharmaceutical composition including a compound of the formula (I) or  
a pharmaceutically acceptable salt or solvate thereof, as claimed in any  
one of the preceding claims, together with a pharmaceutically acceptable  
excipient, diluent or carrier.
25. A compound of the formula (I) or a pharmaceutically acceptable salt,  
solvate or composition thereof, as claimed in any one of claims 1 to 23  
and 24, respectively, for use as a medicament.
26. The use of a compound of the formula (I) or of a pharmaceutically  
acceptable salt, solvate or composition thereof, as claimed in any one of  
claims 1 to 23 and 24, respectively, for the manufacture of a medicament  
to treat a disease for which a A2a receptor agonist is indicated.
27. The use of a compound of the formula (I) or of a pharmaceutically  
acceptable salt, solvate or composition thereof, as claimed in any one of  
claims 1 to 23 and 24, respectively, for the manufacture of an anti-  
inflammatory agent.
28. The use of a compound of the formula (I) or of a pharmaceutically  
acceptable salt, solvate or composition thereof, as claimed in any one of  
claims 1 to 23 and 24, respectively, for the manufacture of a medicament  
for the treatment of a respiratory disease.
29. Use as claimed in claim 28 where the disease is selected from the group  
consisting of adult respiratory distress syndrome (ARDS), bronchitis,  
chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis,  
asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis.
30. The use of a compound of the formula (I) or of a pharmaceutically

acceptable salt, solvate or composition thereof, as claimed in any one of claims 1 to 23 and 24, respectively, for the manufacture of a medicament for the treatment of septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischemia, peripheral vascular disease, post-  
5 ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Helicobacter pylori*-gastritis, non-*Helicobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for  
10 wound healing.

31. A method of treatment of a mammal, including a human being, to treat a disease for which a A2a receptor agonist is indicated including treating said mammal with an effective amount of a compound of the formula (I)  
15 or with a pharmaceutically acceptable salt, solvate or composition thereof, as claimed in any one of claims 1 to 23 and 24, respectively.

32. A method of treatment of a mammal, including a human being, to treat an inflammatory disease including treating said mammal with an effective  
20 amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof, as claimed in any one of claims 1 to 23 and 24, respectively.

33. A method of treatment of a mammal, including a human being, to treat a  
25 respiratory disease including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof, as claimed in any one of claims 1 to 23 and 24, respectively.

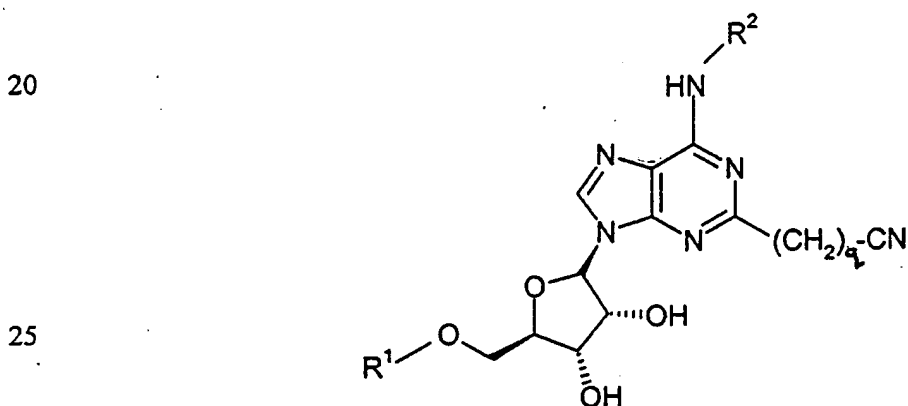
30 34. A method as claimed in claim 33 where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease,



cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis.

35. A method of treatment of a mammal, including a human being, to treat  
5 septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Helicobacter pylori*-gastritis, non-*Helicobacter*  
10 *pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing, including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof, as claimed in any one of claims 1 to 23 and 24,  
15 respectively.

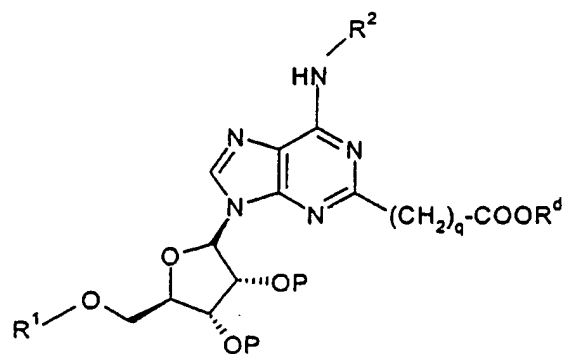
36. A compound of the formula



(IIA);

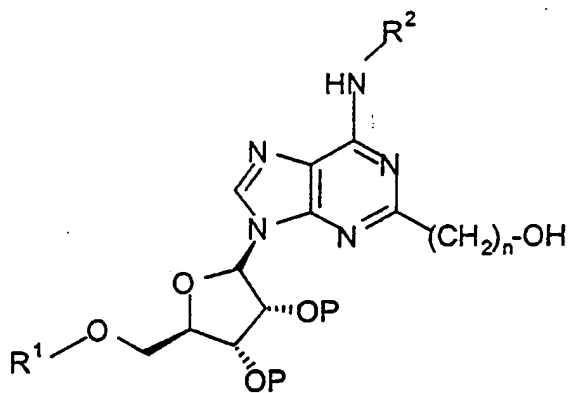
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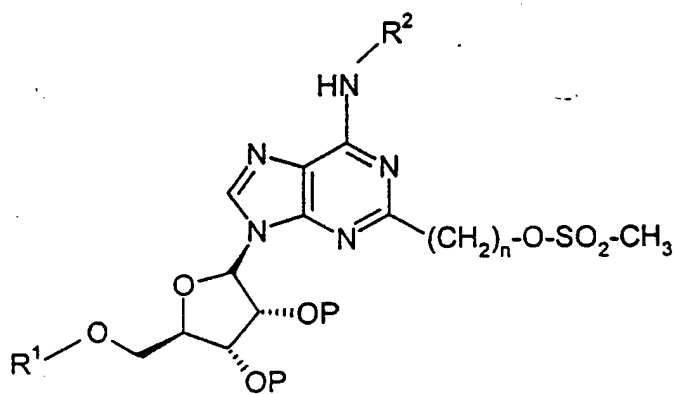


(IIB);

10

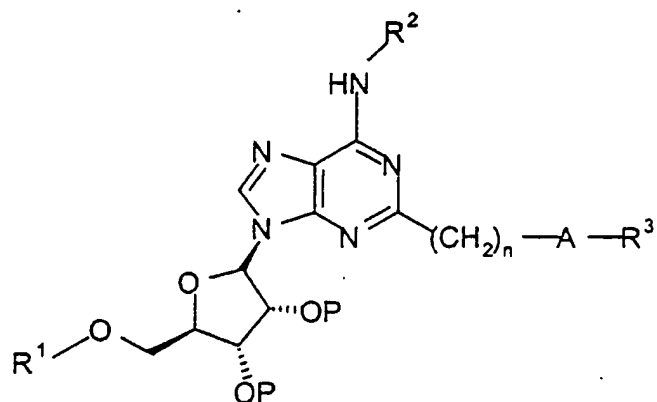


(IB);



(XII),

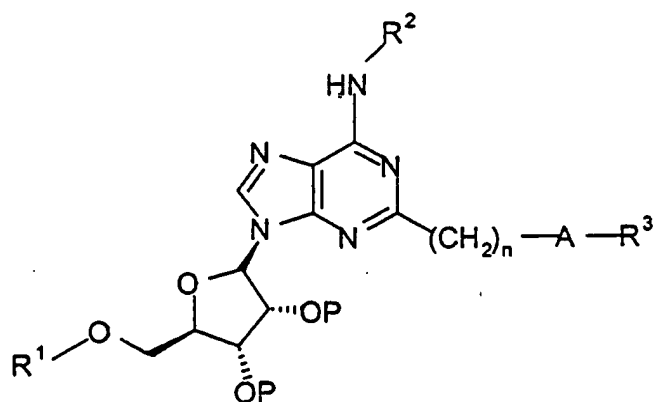
15 or a deprotected form thereof, that is where P is replaced by H; and



(XIII):

- 15 wherein  $q$  is  $n-1$ ,  $R^d$  is H or alkyl (preferably  $C_1$ - $C_6$  alkyl),  $P$  is a protecting group, and  $R^1$ ,  $R^2$ ,  $R^3$ ,  $A$  and  $n$  are as defined in claim 1.

37. A process for the preparation of a compound of the formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt or solvate thereof,  
 20 which comprises  
 (a) for a compound of the formula (I) wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $A$  and  $n$  are as defined in claim 1, deprotection of a compound of the formula

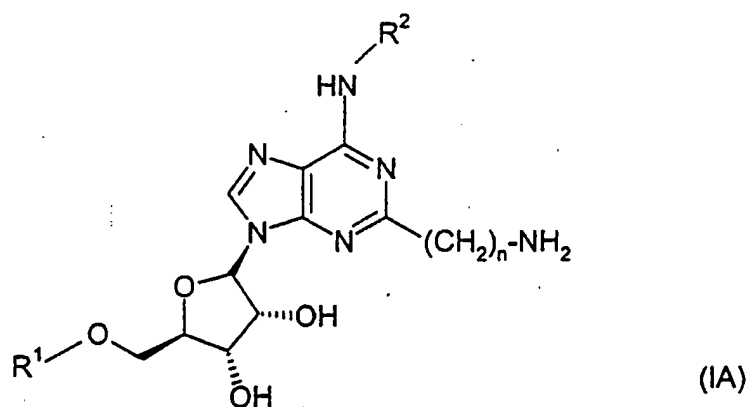


(XIII)

wherein P is a protecting group and  $R^1$ ,  $R^2$ ,  $R^3$ , A and n are as defined in claim 1;

- (b) for a compound of the formula (I) wherein A is  $NR^a$ ,  $NR^aC(O)$ ,  $NR^aC(O)NR^a$ ,  $NR^aC(O)O$  or  $NR^aSO_2$  and  $R^a$ ,  $R^1$ ,  $R^2$ ,  $R^3$  and n are as defined in claim 1, functional group interconversion of a compound of the formula

10

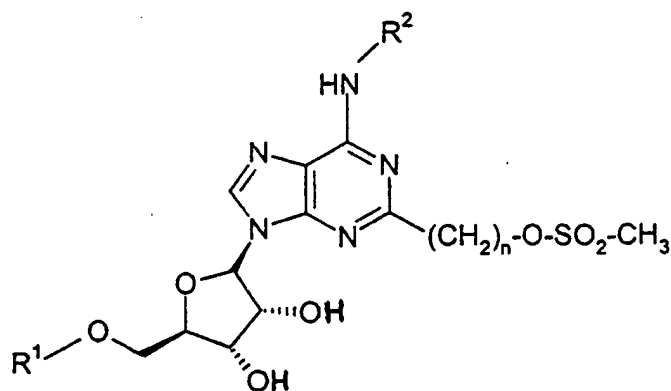


wherein  $R^1$ ,  $R^2$  and n are as defined in claim 1, using an appropriate reagent such as an acylating, sulfonylating or alkylating agent, or a dicarbonate derivative, or by reductive amination; or

20

- (c) for a compound of the formula (I) wherein A is  $NR^aSO_2$ ,  $NR^a$ , O or S and  $R^a$ ,  $R^1$ ,  $R^2$ ,  $R^3$  and n are as defined in claim 1, functional group interconversion of a compound of the formula

25



5

wherein  $R^1$ ,  $R^2$  and  $n$  are as defined in claim 1, using an appropriate reagent such as an alkoxide, thioalkoxide, thiol, sulphonamide derivative or amine : any one of said processes being optionally followed by conversion of the compound of the formula (I) to a pharmaceutically acceptable salt thereof.

10

38. A compound as claimed in claim 1 wherein

$R^1$  is alkyl or cyclopropylmethyl;

15

$R^2$  is phenyl-alkylene or naphthyl-alkylene where the alkylene chain may be substituted with methyl, ethyl, phenyl or naphthyl;

$n$  is 1 or 2; and

20

A is  $NR^a$ ,  $NR^aC(O)$ ,  $NR^aC(O)NR^a$ ,  $NR^aC(O)O$ ,  $OC(O)NR^a$ ,  $C(O)NR^a$ ,  $NR^aSO_2$ ,  $SO_2NR^a$ , O, S or  $SO_2$ , in which  $R^a$  is H or alkyl;

$R^3$  is a group of the formula  $-(CH_2)_p-R^p-B$ , wherein  $p$  is 0, 1 or 2;

25

$R^p$  is a bond, or is alkylene, optionally alkyl-substituted cycloalkylene, phenylene or naphthylene; and

30

B is (i) H,  $-NR^bR^b$ ,  $-OR^b$ ,  $-COOR^b$ ,  $-OCOR^b$ ,  $-SO_2R^b$ ,  $-CN$ ,  $-SO_2NR^bR^b$ ,  $-NR^bCOR^b$  or  $-CONR^bR^b$ , in which each  $R^b$  is the same or different and is selected from H and alkyl, provided that, (a) when B is  $-SO_2R^b$  or  $-NR^bCOR^b$ , then the terminal  $R^b$  is other than H, and, (b)  $R^p$  is a bond,  $p$  is 0 and B is H only when A is  $NR^a$ ,

$\text{NR}^a\text{C}(\text{O})\text{NR}^a$ ,  $\text{C}(\text{O})\text{NR}^a$ ,  $\text{SO}_2\text{NR}^a$ , O or S, or (ii) B is an optionally-substituted, fully or partially saturated or unsaturated mono- or bicyclic heterocyclic group, each of which is linked through a ring carbon atom;

- 5 or a pharmaceutically acceptable salt or solvate thereof.

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/IB 99/01629

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H19/167 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	W0 88 03147 A (WARNER LAMBERT CO) 5 May 1988 (1988-05-05) abstract	1,24-38
A	E.ONGINI ET AL.: "Pharmacology of Adenosine A2A Receptors." TRENDS IN PHARMACOLOGICAL SCIENCE, vol. 17, no. 10, 1996, pages 364-372, XP002123410 the whole document	1,24-38
A	R.RIMONDINI ET AL.: "Adenosine A2A Agonists : A Potential New Type of, Atypical Antipsychotic" NEUROPSYCHOPHARMACOLOGY, vol. 17, no. 2, 1997, pages 82-91, XP000856223 the whole document	1,24-38

-/-

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

22 November 1999

Date of mailing of the international search report

03/12/1999

Name and mailing address of the ISA

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Authorized officer

Scott, J

## INTERNATIONAL SEARCH REPORT

In International Application No.

PCT/IB 99/01629

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	US 5 877 180 A (LINDEN JOEL M ET AL) 2 March 1999 (1999-03-02) the whole document _____	1,24-38



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 99/01629

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 31-35  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 31-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

In. rnational Application No

PCT/IB 99/01629

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8803147 A	05-05-1988	AU 8276187 A DK 357788 A GR 871667 A NO 882887 A	25-05-1988 29-06-1988 03-03-1988 29-06-1988
US 5877180 A	02-03-1999	NONE	